Deficits in Function and Functional Connectivity of Left Occipitotemporal Cortex in Children with Dyslexia

Thesis
presented to the Faculty of Arts
of
the University of Zurich

for the degree of
Doctor of Philosophy

by

Sanne Elisabeth Leonie van der Mark
of The Netherlands

Accepted in the spring semester 2009
on the recommendation of

Prof. Dr. rer. nat. Lutz Jäncke
and
Prof. Dr. Daniel Brandeis

Druckerei Zentrum

Zurich 2009

Contents

Acknowledgement

When I came to Zurich three years ago to start my Ph.D. at the University Children's Hospital and the Department of Child and Adolescent Psychiatry of the University of Zurich, I soon realized that my high and optimistic expectations were even going to be exceeded. Even though it was not always easy, now, at the end of my Ph.D., I can indeed say that the last three years have been a valuable and enrichening experience at both a professional and personal level. I would like to express my gratitude to all those who supported me and gave me the opportunity to complete this work.

First of all, I would like to express my special thanks to two people who made this Ph.D. possible in the first place, and who gave me space to learn. I would like to thank Prof. Dr. Daniel Brandeis for offering me the possibility to write my Ph.D. thesis in his interesting and relevant longitudinal dyslexia project, for offering me solid scientific advice and guidance, and for supporting me during the last three years. Also, I would like to thank Prof. Ernst Martin for giving me the possibility to accomplish this Ph.D. thesis, for sharing his vision on science, for his valuable advice, and for providing the infrastructure at the MR-Center of the University Children's Hospital.

I would like to express my deepest gratitude to Dr. Kerstin Bucher for her excellent and extensive support and her invaluable guidance throughout my Ph.D. thesis. Thank you very much! Furthermore, my very special thanks go to Dr. Peter Klaver for his valuable contribution to my Ph.D. thesis. I am grateful to him for sharing his profound scientific knowledge, for his encouragement, for believing in me, and for the many scientific, psychological and philosophical discussions that have been a source of inspiration to me.

I would like to express further greatest thanks to my collaboration partner Enrico Schulz who did his Ph.D. on the same project. It was a pleasure to work with him. My warmest thanks go to Dr. Urs Maurer for his expertise and excellent guidance throughout my Ph.D. and to Dr. Silvia Brem for her great scientific support.

I would also like to express my gratitude to my colleagues at the MR-Center and the Department for Child and Adolescents Psychiatry for their help, encouragement, and fruitful conversations: Karin Kucian, Mengia Dosch, Stephanie Rotzer, Janine Lichtensteiger, Beat Werner, Thomas Loenneker, Silvia Bach, Lilian Valko and Antonia Seitz.

My gratitude also goes to my promoter Prof. Dr. Lutz Jäncke for giving me the opportunity to complete this thesis.

I am also deeply grateful to my parents for their never-ending support and encouragement. Thank you for always believing in me. A big Thank You also goes to all my friends in Zürich and back home (you know who I mean), who supported me all these years and never lost faith in me. Thank you for listening and sharing!

Last, but not least, I would like to thank all the children and their parents who participated in the experiments. This work would not have been possible without their curiosity, patience and willingness to participate in the sometimes extensive testing sessions. It was a true pleasure to meet you and work with you.

Summary

Reading is of enormous importance in our modern information-based society and an essential activity in everyday life. While most children successfully learn to read within a few years, reading acquisition is severely impaired in about 5-10% of children, resulting in a specific reading disorder called "developmental dyslexia". One of the core deficits of individuals with dyslexia is impaired automatic word recognition, which leads to slow, dysfluent reading. Neuroimaging studies in adult readers have linked this orthographic processing deficit to deficits in a specific section of the left occipitotemporal cortex (the visual word form area; VWFA) involved in visual word processing. However, the exact function of the VWFA and the larger left occipitotemporal VWF-system in healthy children, as well as its dysfunctioning in dyslexic children is still unclear. In addition, since the VWF-system and its core region (the VWFA) are part of the typical language network that encompasses several other regions crucially involved in reading, there is considerable interest in examining the connectivity between those brain areas

This Ph.D. thesis aimed to investigate both the function and functional connectivity comparing control children and children with dyslexia. In *Study A* we examined (i) two levels of functional specialization of visual word processing − (a) coarse specialization for print and (b) sensitivity to orthographic familiarity of letter strings − in the left occipitotemporal VWF-system in control children, and (ii) whether these types of specialization were impaired in children with dyslexia. In *Study B* we investigated (i) the functional connectivity of the VWF-system and other major components of the language network in control children, and (ii) whether these connections were different in dyslexic children.

We tested 18 dyslexic and 24 age-matched control children (age 9.7-12.5 years) while they indicated if visual stimuli (real words, pseudohomophones, pseudowords and false-fonts) sounded like a real word. Five adjacent regions of interest (ROIs) in the bilateral occipitotemporal cortex were selected to cover the full anterior-posterior extent of the VWF-system. In Study A, we used functional MRI to assess the brain activity in

response to four types of visual letter strings varying in orthographic familiarity. In Study B, we used functional connectivity MRI to examine interregional cooperation within the language network, focussing on the VWFA.

The results from Study A revealed that control children show a dissociation of two functional levels of specialization within the VWF-system: (1) coarse specialization for print, i.e. different processing of letter strings than of visual control stimuli and (2) sensitivity to orthographic familiarity of letter strings. Furthermore, we showed that both of these functional levels of VWF-system specialization could not be detected in children with dyslexia in the entire VWF-system. To answer the question whether this functional impairment of the VWF-system is associated with impaired cooperation of this system with other language areas, we looked at the functional connectivity of these regions. The results from Study B revealed that, in control children, the functional connections with typical language areas (left inferior parietal lobule and left inferior frontal gyrus) were specific for the VWFA and did not generalize to left occipitotemporal regions neighbouring the VWFA. In addition, we demonstrated that these functional connections between the VWFA and other major language areas are disrupted in children with dyslexia, whereas those of neighbouring areas were not affected.

The results of both studies reveal an impairment of both function (of the VWF-system) and functional connectivity (of the VWFA with left inferior parietal and inferior frontal cortex) in dyslexic children. In conclusion, the findings presented in this work demonstrate that (1) word processing deficits in dyslexic children are associated with a pervasive developmental dysfunction of the entire VWF-system, and that (2) brain regions necessary for fluent, skilled reading may not work together properly during reading.

Zusammenfassung

Das Lesen hat einen erheblichen Stellenwert in unserer modernen informationsbasierten Gesellschaft und ist im Alltag unerlässlich. Während die meisten Kinder innerhalb von wenigen Jahren erfolgreich lesen lernen, ist das Erwerben der Lesefähigkeit bei ungefähr 5-10% aller Kinder beeinträchtigt. Die daraus resultierende spezifische Lesestörung wird „entwicklungsbegingte Dyslexie“ genannt. Eines der Kerndefizite von Kindern mit Dyslexie ist die Beeinträchtigung der automatisierten Worterkennung, welche zu einer verlangsamten, stockenden Leseweise führt. Neuroimaging Studien von erwachsenen Lesern haben dieses orthographische Defizit mit der funktionellen Störung des linken occipitotemporalen Kortexes, der für die visuelle Wortverarbeitung zuständig ist, in Verbindung gebracht (engl.: visual word form area; VWFA). Die genaue Funktion des VWFA und des gesamten linken occipitotemporalen VWF-Systems von gesunden Kindern sowie deren Dysfunktion bei Kindern mit Dyslexie sind bislang noch unklar. Das VWF-System inklusive deren Kernregion (VWFA) sind Bestandteil des Sprachverarbeitungsnetzes, das sich aus verschiedenen Bereichen des Gehirns zusammensetzt. Es besteht ein grosses Interesse daran, die Vernetzung innerhalb und zwischen diesen Gehirnregionen (funktionale Konnektivität, engl.: functional connectivity) zu untersuchen.

Ziel der vorliegenden Doktorarbeit war es, sowohl die Funktion der VWFA als auch die Verbindungen des Sprachverarbeitungsnetzes von Kindern mit und ohne Dyslexie zu vergleichen. In *Studie A* untersuchten wir (i) zwei Stufen der funktionellen Spezialisierung der visuellen Wortverarbeitung – (a) die grobe Spezialisierung für Schrift und (b) die Spezialisierung bezüglich der orthographischen Vertrautheit der Zeichenketten – im linken occipitotemporalen VWF-System von Kontrollkindern. Weiterhin untersuchen wir (ii) ob diese Spezialisierungen in Kindern mit Dyslexie beeinträchtigt sind. In *Studie B* untersuchten wir (i) die funktionelle Konnektivität des VWF-Systems und anderer Bereiche des Sprachverarbeitungsnetzes in Kontrollkindern und (ii) ob sich diese Verbindungen von denen von Kindern mit Dyslexie unterschieden.

Wir untersuchten 18 Kinder mit Dyslexie und 24 Kontrollkinder der vierten und fünften Klasse (9.7-12.5 Jahre). In einem Experiment bestand die Aufgabe, zu entscheiden, ob visuell dargebotene Zeichenketten (reale Wörter, pseudohomophone Wörter, Pseudowörter und Symbolketten) wie ein wirkliches, im Deutschen existierendes Wort klingen oder nicht. Es wurden 5 benachbarte Regionen im linken und rechten occipitotemporalen Kortex definiert, die die gesamte anterior-posteriore Ausdehnung des VWF-Systems abdeckten.

Aus Studie A ging hervor, dass Kontrollkinder eine zweidimensionale funktionelle Spezialisierung innerhalb des VWF-Systems aufweisen: (1) eine grobe Spezialisierung für Schrift, d.h. unterschiedliche Zeichenketten wurden unterschiedlich verarbeitet, und (2) eine Spezialisierung bezüglich der orthographischen Vertrautheit der Zeichenketten. Es zeigte sich ausserdem, dass diese beiden Bereiche der Spezialisierung im VWF-System von Kindern mit Dyslexie nicht nachgewiesen werden konnten. Zur Beantwortung der Frage, inwieweit diese Funktionsbeeinträchtigung des VWF-Systems mit einer Beeinträchtigung der Kommunikation mit anderen Sprachbereichen verbunden ist, untersuchten wir die funktionelle Konnektivität innerhalb des Sprachverarbeitungsnetzwerkes. Die Resultate von Studie B zeigten, dass bei Kontrollkindern funktionelle Verbindungen von Hirnregionen, die an der Sprachverarbeitung beteiligt sind (linker inferiorer Parietallappen und linker inferior-frontaler Gyrus) ausschliesslich zum VWFA angelegt waren und nicht zu benachbarten Regionen des linken occipitotemporal VWFA weiterführten. Zudem zeigte sich, dass diese funktionellen Verbindungen zwischen dem VWFA und anderen wichtigen Sprachareale bei Kindern mit Dyslexie beeinträchtigt waren, wohingegen die der benachbarten Regionen im VWF-System nicht beeinträchtigt waren.

Die Resultate beider Studien zeigen Beeinträchtigungen sowohl der Funktion (des VWF-Systems) als auch der funktionellen Konnektivität innerhalb des Sprachnetzwerkes bei Kindern mit Dyslexie auf.

Dies bedeutet, dass (1) Textverarbeitungsdefizite in Kindern mit Dyslexie mit einer Entwicklungsfunktionsstörung des gesamten VWF-Systems verbunden sind, und dass zusätzlich die Interaktion (2) dieser für flüssiges und geübtes Lesen notwendigen Hirnregionen beeinträchtigt ist.

1. Introduction

Reading is of enormous importance in our modern information-based society, in which continuous acquisition of knowledge has become necessary for keeping pace with fast global changes. Furthermore, good reading skills are the most significant factor in academic success, since most knowledge and information, but also stories and poems, are transferred from one reader to another and from one generation to the next by books and other forms of written texts. Despite its importance, reading is not an inborn ability and has to be learned through extensive training at school, usually starting in the first year that children go to school (at age 5-7 years). With the start of reading acquisition, specific brain regions begin to take on functions required for processing written words, and a specialized reading network is established (Maurer, Brem et al. 2005). However, about 5-10% of children have severe impairments in learning to read, resulting in a specific reading disorder called “developmental dyslexia”.

Developmental dyslexia is characterized by an unexpected difficulty in reading in children and adults who otherwise possess the intelligence and motivation considered necessary for accurate and fluent reading. Such difficulties in learning to read or losing this ability as a result of a neurological disorder often lead to individual tragedies and social costs. Specifically, dyslexic individuals typically have difficulties with fluent recognition of printed words, spelling and letter-sound decoding (Lyon, Shaywitz et al. 2003). While, in the past decade, a great deal has become known about the deficits in phonological processing (letter-sound decoding) that form the core impairment of dyslexia, little is yet known about the deficits in orthographic processing (fluent recognition of visual words). In addition, most previous studies investigating dyslexia have focussed on examining dyslexia in adults rather than in children with little reading experience and of whom it is unlikely that they have already developed compensatory strategies to deal with their disorder. As a consequence, these studies could not determine whether deficits in orthographic processing constitute a fundamental problem in dyslexia or is simply the result of

compensation. Therefore, in order to truly understand the neurobiology of dyslexia, it is crucial to examine young children in the early stages of reading acquisition.

The goal of the present thesis is to evaluate the neural mechanisms underlying orthographic processing in children with developmental dyslexia. In a first step, we systematically investigated whether a neural system, known to be critically involved in skilled reading, is dysfunctional in children with dyslexia. In a second step, we analyzed whether functional cooperation between this neural system and other major components of the traditional language network were disturbed in dyslexic children.

But first, before starting with the experimental part, let me briefly introduce the methods used in this thesis: functional magnetic resonance imaging and functional connectivity magnetic resonance imaging. This section is followed by a short overview of the neural correlates of skilled reading and an introduction to the principal topic of this thesis: developmental dyslexia. After the description of our experiments and results, a general discussion of the findings of the two studies will conclude this thesis.

2. Magnetic Resonance Imaging

This chapter gives a short introduction into the methods used in Experiment 1 and 2. The principles of functional magnetic resonance imaging and functional connectivity magnetic resonance imaging are explained.

2.1 Functional Magnetic Resonance Imaging

Within the past decade, functional Magnetic Resonance Imaging (fMRI) has become the dominant research technique in cognitive neuroscience. This technique provides images of brain regions that are 'activated' during performance of a specific task, by measuring the hemodynamic response related to neural activity in the brain. The time course of the fMRI hemodynamic response (see Figure 2.1) takes advantage of the fact that oxygenated and deoxygenated haemoglobin have differential magnetic properties: deoxy-haemoglobin is paramagnetic whereas oxy-haemoglobin is diamagnetic. In case of specific information processing in brain regions, neurons become activated and a subsequent increase of local cerebral blood flow is needed to meet these regions' increased need for glucose and oxygen. After an initial decrease of oxy-haemoglobin due to the consumption of oxygen (initial dip) there is a large increase in blood flow and therefore an increase in oxy-haemoglobin in relation to deoxy-haemoglobin is observed. The oxygen supply has been demonstrated to overcompensate the neuronal need (Fox and Raichle 1986), reaching its peak at 5-8 seconds after the stimulus onset. The overcompensation results in an increase in the ratio between oxygenated and deoxygenated blood. Owing to the different magnetic properties of oxygenated and deoxygenated haemoglobin, the so called "Blood-Oxygen-Level-Dependent" (BOLD) contrast (Ogawa, Lee et al. 1990) arises, corresponding to an increase in the MR-signal. Finally, the oxy-deoxy-haemoglobin ratio decreases back to below baseline again only after 10-16 seconds (post-stimulus undershoot), because after the oversupply of oxygenated blood has diminished, it still takes some time for the blood volume to return to baseline.

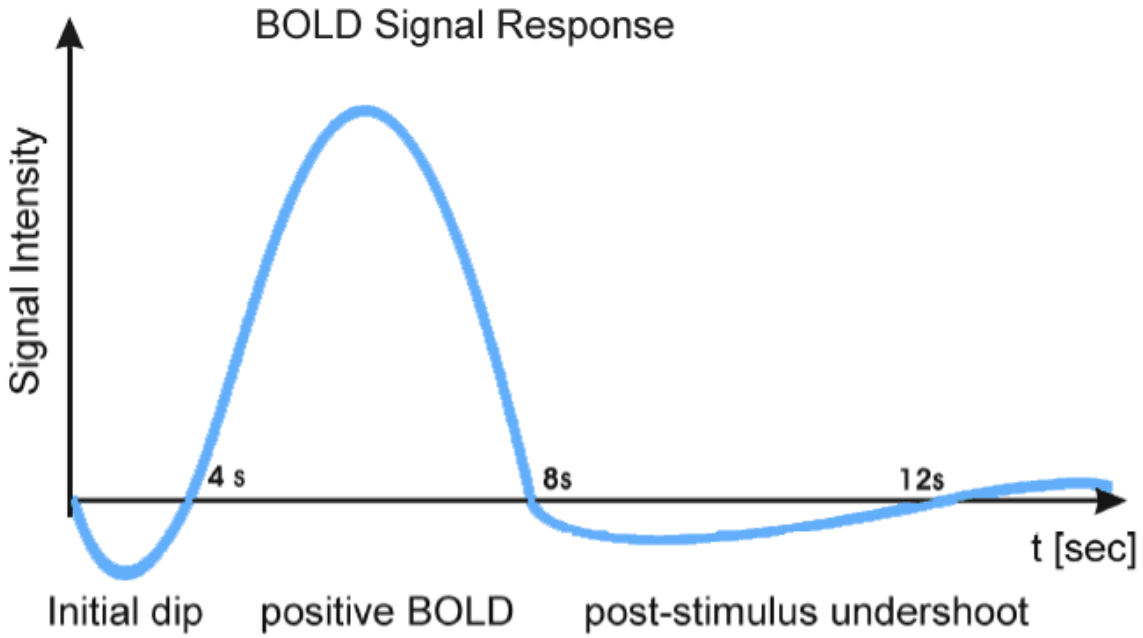


Figure 2.1. The time course of the hemodynamic response (Jäncke 2005).

Like any other technique, fMRI has strengths and limitations. Since the fMRI method is non-invasive – in contrast to positron emission tomography (PET) for example, which relies on radioactive injections – it can be repeated as many times as needed in the same individual and is suitable for investigating the brain function of children. Also, fMRI has a good spatial resolution of about 3 mm due to the spatial specificity of the BOLD-response. On the other hand, in comparison to techniques such as electroencephalography (EEG), it has a poor temporal resolution (> 1 sec) because the BOLD-effect is observed only after several seconds. In addition, due to the correlative nature of the analysis, fMRI cannot draw causal links between abnormal activation in a certain brain area and deficits of a disorder (such as dyslexia). This is different from neuropsychological studies of patients with lesions demonstrating that damage to a brain area is followed by the appearance of a specific deficit. Furthermore, since fMRI measures hemodynamic changes rather than spiking activity of neurons, it provides only an indirect measure of neuronal activity. However, the tight coupling between neuronal activity and oxygen consumption is widely acknowledged and partly proven (Logothetis, Pauls et al. 2001; Logothetis and Wandell 2004). A further limitation of this method is its dependency on the

calculation of a contrast, i.e. the comparison of a condition with baseline, or a contrast between conditions or groups. This is another reason why fMRI, compared to PET and EEG, is an indirect measure of brain activity. Moreover, most fMRI studies use hypothesis-driven analyses that have the potential problem that they require an accurate estimate of the fMRI signal that should result from the performance of the task. However, the assumptions of hypothesis-driven analyses may not always be valid. In addition, fMRI has often been used to show activation localized to specific regions, thus ignoring the distributed nature of processing in neural networks. These last three limitations are due to the nature of the traditional univariate fMRI technique. However, they can be addressed by a recent multivariate statistical technique: functional connectivity magnetic resonance imaging (fcMRI). This technique allows researchers to work around these issues by characterizing interactions between 'active' regions discovered via traditional univariate techniques.

2.2 Functional Connectivity Magnetic Resonance Imaging

As mentioned above, most fMRI studies applied conventional hypothesis-driven analyses in order to localize where modulation of the BOLD-signal is attributable to the experimental paradigm. However, analysis of functional connectivity between brain region using fMRI data may contribute significantly to a better understanding of the cooperation between regions within large-scale neural networks. Because the fMRI signal has a temporal signature, information about the coherence of activity over time can be used to create functional connectivity maps. These maps describe the pattern of functional relations among brain regions, independent of particular stimulus-related activation. Functional connectivity has been defined as low-frequency (<0.1 Hz) temporal correlation between spatially remote neurophysiological events (Horwitz, Grady et al. 1992; Friston, Frith et al. 1993; Biswal, Yetkin et al. 1995; Friston 1995; Lowe, Mock et al. 1998; Xiong, Parsons et al. 1999; Arfanakis, Cordes et al. 2000; Cordes, Haughton et al. 2000; Fox and Raichle 2007). Although this technique is limited in its

ability to determine the directionality or strength of connections (Buchel and Friston 2000; Horwitz and Braun 2004) it can reveal functional interactions (Friston, Frith et al. 1996). This is different from effective connectivity analyses that test for unidirectional modulatory influences of a small number of brain region upon another, which are defined in a model based on prior knowledge (e.g.,(Friston 1994; Bitan, Booth et al. 2005; Cao, Bitan et al. 2008)). Compared to effective connectivity, functional connectivity has the advantage that it is a data-driven rather than a hypothesis-driven type of analysis, thus not reducing its validity to the validity of the model (Friston 1994). For a more elaborate discussion of advantages and disadvantaged of the method see Fox and Raichle (2007).

FcMRI can be assessed in a number of ways and has been used to assess a wide range of conditions (for a review see, Horwitz, 2003). In study B, we used a method called seed-voxel correlation mapping (Horwitz, Grady et al. 1992; Biswal, Yetkin et al. 1995), in which the BOLD time course from a region of interest (called a seed region) is extracted and then the temporal correlation between this extracted signal and the time course from all other brain voxels is determined (see Figure 2.2). Seed-voxel correlation mapping has become popular because of its inherent simplicity, sensitivity and ease of interpretation (e.g., (Lowe, Mock et al. 1998; Xiong, Parsons et al. 1999; Cordes, Haughton et al. 2000; Cordes, Haughton et al. 2001; Hampson, Peterson et al. 2002; Fox, Snyder et al. 2006)).

Finally, there is some indication that a disruption in functional connectivity may be linked to a disruption of anatomical connections. Studies investigating brain morphometry in individuals with dyslexia using diffusion tensor imaging (Klingberg, Hedehus et al. 2000; Beaulieu, Plewes et al. 2005; Deutsch, Dougherty et al. 2005; Niogi and McCandliss 2006; Niogi and McCandliss 2006) and voxel-based morphometry (Eckert, Leonard et al. 2005; Silani, Frith et al. 2005) have associated dyslexia with changes in anatomical connections of temporoparietal regions. Such anatomical abnormalities would become visible in fcMRI as functional disconnections between cortical regions, since they would affect neuronal transmission that would subsequently affect the synchrony of the BOLD signal (Poldrack 2001). However, future studies combining techniques for examining

functional and anatomical connections would be necessary to better understand the neurobiological basis of a pathological disruption in functional connectivity.

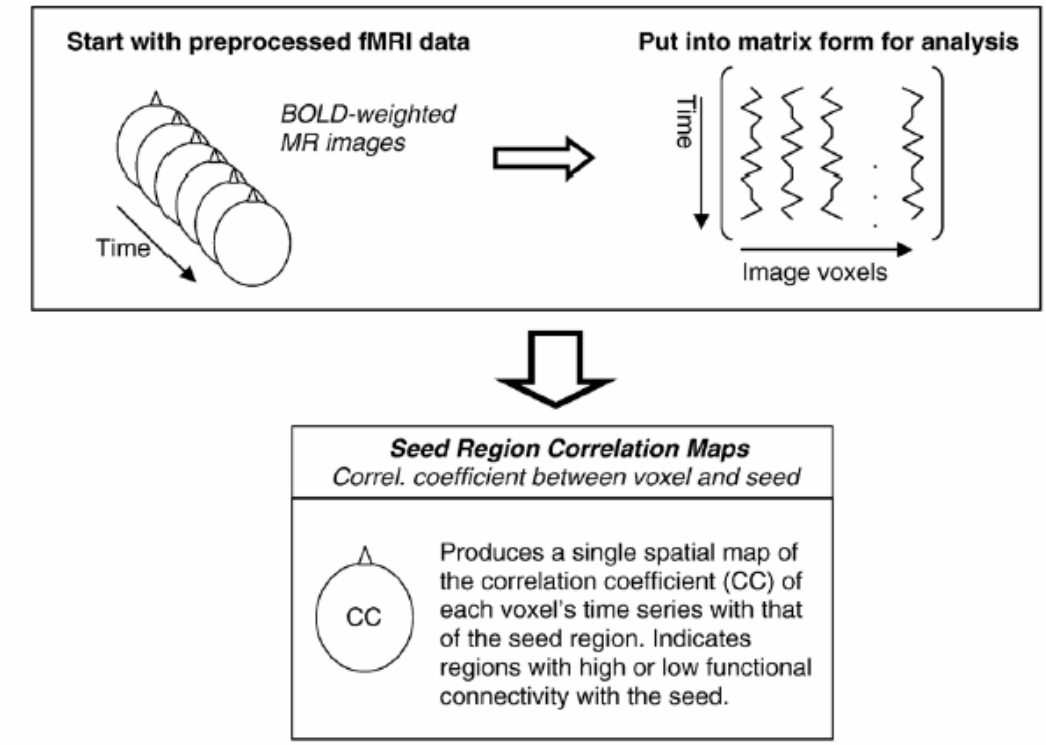


Figure 2.2. Seed-voxel correlation approach used for mapping connectivity in the whole brain using fMRI time-series data (Rogers, Morgan et al. 2007).

3. Neural Correlates of Skilled Reading

This section introduces the neural correlates of skilled reading and discusses the functional and anatomical specialization of the left occipitotemporal cortex as well as connections with other major language processing areas.

Skilled reading requires fast visual brain processes specialized for the visual word form. The visual word form (VWF) (Warrington and Shallice 1980) is an abstract representation of letter strings (extracted from the retinal stimulus) that is invariant for changes in size, position, font, or case. It is computed by a number of visual processes that are not innate but that can be acquired only after years of training (Aghababian and Nazir 2000). Neuroimaging studies (for a review, see (Jobard, Crivello et al. 2003)) and neuropsychological testing of patients with pure alexia (Cohen, Martinaud et al. 2003; Cohen, Henry et al. 2004; Henry, Gaillard et al. 2005) have demonstrated that a section of the left inferior occipitotemporal cortex, the midfusiform gyrus, plays a vital role in such specialized visual word processing. This resulted in the classification of this brain region as the 'visual word form area' (VWFA) (Cohen, Dehaene et al. 2000). This area was shown to activate more strongly for visually presented words than for checkerboards (Cohen, Lehericy et al. 2002), to process letter strings in a fast manner – within 200 ms after stimulus onset (Tarkiainen, Helenius et al. 1999) – and may relay an abstract representation of the visual word form to higher-order areas of the traditional language network. Across neuroimaging studies, the activation peak of the VWFA is consistently found at the same location in Talairach space (approximately x = -43; y = -54; z = -12), with a standard deviation of about 5 mm (Cohen, Dehaene et al. 2000). The emergence of VWFA specialization has been related to experience and training. In nonimpaired children, this area was found to progressively develop, through acquisition of reading experience, into a specialist region for visual word recognition (Shaywitz, Shaywitz et al. 2002; McCandliss, Cohen et al. 2003; Maurer, Brem et al. 2006; Shaywitz, Skudlarski et al. 2007).

3.1 Functional Specialization of the Left Occipitotemporal Cortex

The exact function of the VWFA in visual word processing is still under debate, since fMRI studies provide inconsistent results. While some studies found that words evoke stronger activation in the VWFA than visual control stimuli such as checkerboards (Cohen, Lehericy et al. 2002), false-fonts (Vinckier, Dehaene et al. 2007), or pictures (Gauthier, Tarr et al. 2000; Hasson, Levy et al. 2002), other studies found similar activation for both words and false-fonts (Tagamets, Novick et al. 2000; Brem, Bucher et al. 2006). In addition to these findings of a fast, coarse form of visual tuning for print (letter strings vs. visual control stimuli), a second type of VWFA specialization has been proposed. A recent study investigating VWFA processing at the whole-word level presented adults and adolescents with three types of letter strings with varying orthographical familiarity (Kronbichler, Bergmann et al. 2007; Bruno, Zumberge et al. 2008). The results demonstrated that pseudohomophones (phonologically familiar but orthographically unfamiliar forms of real words) and pseudowords (phonologically and orthographically unfamiliar word-forms without semantic content) evoked stronger activation than real words in the VWFA. This finding indicates that the VWFA processes familiar word-forms more efficiently than unfamiliar word-forms. The authors referred to this effect as the "orthographic familiarity effect" (Kronbichler, Bergmann et al. 2007; Bruno, Zumberge et al. 2008). They proposed that the VWFA may serve as an orthographic input lexicon, where incoming letter strings are compared with orthographic lexicon entries (Bruno, Zumberge et al. 2007; Kronbichler, Bergmann et al. 2007). Whereas familiar words are able to access word associations stored in memory without much effort, the stronger activation for the orthographically unfamiliar stimuli demonstrates that they require a substantial amount of effort (in the case of PH) or even fail to access these associations (in the case of PW). Therefore, the finding of reduced activity for familiar words in comparison to unfamiliar word-forms may reflect a VWFA specialization for highly automated processing of printed words, at a whole-word level.

3.2 Anatomical Specialization of the Left Occipitotemporal Cortex

In addition to the exact function of the VWFA, another issue that is still a topic of debate is whether visual tuning to words is confined to the VWFA or whether it also involves other areas within a larger system within the left occipitotemporal gyrus (the VWF-system). While most previous neuroimaging studies have focused on the VWFA, recent findings indicate that, in adults and adolescents, regions differ in their specificity for letter string processing depending on their position on the posterior-anterior axis of the occipitotemporal gyrus (Brem, Bucher et al. 2006; Vinckier, Dehaene et al. 2007). Furthermore, in line with findings from single unit recordings in non-human primates during visual object perception (for review: (Ungerleider and Haxby 1994)), neuroimaging studies in humans have provided indications for the existence of a hierarchy for visual word processing in this left-hemispheric ventral brain system, progressing from simple letter percept to more complex word semantics (Puce, Allison et al. 1996; Vandenberghe, Price et al. 1996; Indefrey, Kleinschmidt et al. 1997; Hagoort, Indefrey et al. 1999; Tarkiainen, Helenius et al. 1999; Cohen, Dehaene et al. 2000; Fernandez, Heitkemper et al. 2001). However, since these studies have investigated adults, the contribution of various regions within the VWF-system during orthographic processing in young children is still unclear.

4. Developmental Dyslexia

In this chapter the term 'developmental dyslexia' is introduced together with its aetiology. Further, a description of the neural correlates of the orthographic processing deficit of this reading disorder is given.

4.1 Definition

The term 'developmental dyslexia' (hereafter referred to as **dyslexia**) indicates a severe, specific disorder of reading acquisition (Schulte-Körne 2001). Dyslexic individuals typically have difficulties with fluent recognition of printed words, spelling and letter-sound decoding (Lyon, Shaywitz et al. 2003). These reading deficits are generally considered to be independent of overall intelligence and motivation and not directly attributable to sensory difficulties or educational deprivation (Dilling, Mombour et al. 1993). Dyslexia is probably the most common neurobiological disorder affecting children, with prevalence rates ranging from 5 to 10 percent (Schulte-Körne 2001). It is a persistent, chronic condition rather than a transient developmental delay (Figure 4.1), meaning that, as time passes, differences in reading skills between good and poor readers tend to stay approximately the same (Shaywitz and Shaywitz 2005).

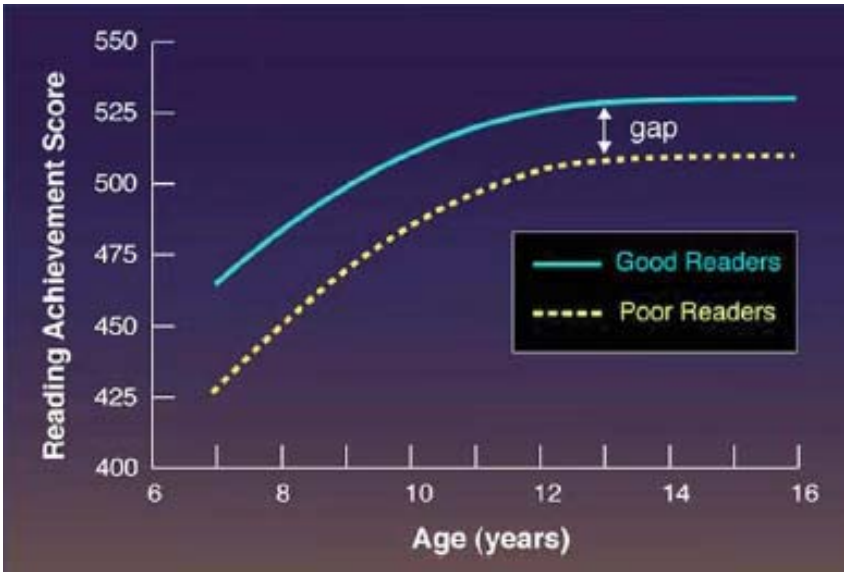


Figure 4.1. Trajectory of eading skills over time in nonimpaired and dyslexic readers. Both dyslexic and nonimpaired readers improve their reading scores as they get older, but the gap between the dyslexic and nonimpaired readers remains (Shaywitz 2003).

4.2 Aetiology

Dyslexia is both familial and heritable (Pennington and Gilger 1996). Due to a genetic component (Schumacher, Hoffmann et al. 2007), dyslexia is persistent over time and can continue into adolescence regardless of enormous treatment efforts (Bruck 1992; Shaywitz, Fletcher et al. 1999). Four language related variables (phonological awareness, sentence imitation, letter identification, rapid naming) and the mother's education have been identified as relevant for future reading abilities (Catts, Fey et al. 2001). Furthermore, environmental factors such as the orthographic consistency of the language system can also add to the prevalence of dyslexia, meaning that recognition of dyslexia is variable across languages (Landerl, Wimmer et al. 1997; Paulesu, McCrory et al. 2000). Specifically, reading impairments are less common in languages with a consistent and shallow orthography (e.g. Italian and German), compared to languages containing inconsistent and deep orthography (e.g. English and French) where dyslexic children suffer from much greater impairments in reading acquisition (Landerl, Wimmer et al. 1997; Paulesu, McCrory et al. 2000). The link between genetic contributions of dyslexia and environmental factors as well as how they relate to functional brain processes is still unknown.

4.3 Neural Correlates of Orthographic Processing Deficits in Dyslexia

The phonological deficit theory is the leading theory of dyslexia, among the large number of theories of dyslexia that exist (including theories of visual, auditory, and cerebellar deficits). It postulates that individuals with dyslexia are not able to access the underlying sound structure of words (Ramus, Rosen et al. 2003). These deficits and the corresponding left superior posterior temporal underactivation during demanding verbal tasks remain the most diagnostic and prominent findings in many neuroimaging studies (Shaywitz, Shaywitz et al. 2002; Simos, Breier et al. 2002). However, next to this well-documented phonological core deficit in dyslexia, converging evidence indicates the existence of another major deficit in individuals with dyslexia: deficits in orthographic processing of visual words. Since fast, orthographic recognition of words is crucial for automatic reading, impaired

orthographic processing of visual words prevents skilled, fluent reading. This orthographic deficit has been linked to deficits in the left occipitotemporal cortex that seem to be about equally robust as the phonological deficits, and may be especially closely related to fluency and reading speed.

To date, few brain imaging studies have investigated the function of the left occipitotemporal gyrus in impaired adult readers and even fewer have examined children with dyslexia. Functional brain imaging studies using positron emission tomography (PET) (Rumsey, Horwitz et al. 1997; Rumsey, Nace et al. 1997; Horwitz, Rumsey et al. 1998; Brunswick, McCrory et al. 1999; Paulesu, Demonet et al. 2001; McCrory, Mechelli et al. 2005), fMRI (Shaywitz, Shaywitz et al. 2003; Kronbichler, Hutzler et al. 2006; Wimmer, Kronbichler et al. under revision), and magnetoencephalography (MEG) (Salmelin, Service et al. 1996; Helenius, Tarkiainen et al. 1999) found the VWFA to be underactivated in dyslexic individuals compared to controls during word reading tasks. However, few studies so far have found an underactivation in the left occipitotemporal gyrus in children with dyslexia (Shaywitz, Shaywitz et al. 2002; Cao, Bitan et al. 2006; Maurer, Brem et al. 2007; Shaywitz, Skudlarski et al. 2007).

Recently, Shaywitz and colleagues (2007) proposed that the difference between children with and without dyslexia is their ability to increasingly engage the left occipitotemporal cortex (Shaywitz, Skudlarski et al. 2007). They go on to suggest, that this VWFA dysfunction may lead to a failure to acquire the efficiency and automaticity of visual word processing which is typical of skilled reading. Support for this hypothesis comes from a recent longitudinal ERP study investigating the emergence of specialization of visual brain regions for print in pre-school children who had a familial risk of developing dyslexia and in age-matched children without a familial risk. These children were measured before and after receiving first reading instruction in school (Maurer, Brem et al. 2007). The results revealed that the occipitotemporal N1 response at 150-270 ms was stronger for words than for symbol strings and that this effect was reduced in the children who developed dyslexia. These findings provide first indications that delayed early visual specialization for print plays a crucial role in the development of dyslexia. However, these neuroimaging studies compared words with symbol

strings or non-words (sub-lexical processing), whereas no study so far has investigated the effects of dyslexia on VWFA specialization in impaired children with stimuli varying in their orthographic similarity to real words (whole-word processing). Furthermore, most previous studies of dyslexia have focused on the VWFA and none so far have examined in a systematical manner whether left occipitotemporal regions neighbouring the VWFA are also impaired.

4.4 Disrupted Connectivity with Major Language Processing Areas

Findings from neuroimaging studies with conventional fMRI analyses demonstrate that in dyslexia multiple brain regions of the language network fail to work together properly during reading (Maisog, Einbinder et al. 2008). While these conventional fMRI studies are restricted to the localization of brain regions involved in dyslexia (due to the nature of the activation analyses), there is considerable interest in examining the connectivity between those brain areas. Yet, previous studies investigating dyslexia-related changes in functional connectivity (fcMRI) within the language network focused on left angular gyrus (Horwitz, Rumsey et al. 1998; Pugh, Mencl et al. 2000) and on functional connectivity in adults with dyslexia (Horwitz, Rumsey et al. 1998; Pugh, Mencl et al. 2000; Shaywitz, Shaywitz et al. 2003; Stanberry, Richards et al. 2006). Findings from these fcMRI studies indicate a disruption of the functional connectivity between left occipitotemporal, parietotemporal and left inferior frontal regions essential for fluent reading. These findings are supported by a recent effective connectivity study in children with dyslexia during a visual word rhyming task (Cao, Bitan et al. 2008). However, compared to functional connectivity analyses, effective connectivity methods are more dependent on a previously defined model, thereby limiting the validity of their conclusions to the validity of the model. Consequently, more research is needed in order to clarify the exact nature of the disruptions in connectivity in children who suffer from dyslexia.

5. General Aims and Hypotheses

In this chapter, the general aims and hypotheses that were developed for the two studies of this thesis will be described.

Two complementary brain imaging tools (fMRI and fcMRI) were applied to investigate the neurobiological basis of dyslexia, focussing on dysfunction and functional disconnection of the Visual Word Form-System.

General aim 1 (Study A): To examine, by means of fMRI, whether a possible dysfunction of specialization within the VWF-system for processing print and orthographic familiarity is already present in young children with dyslexia.

Hypotheses: We expected control children to show a dissociation of two *functional* levels of specialization within the VWF-system: (1) coarse specialization for print, i.e. differential processing of letter strings (real words, pseudohomophones and pseudowords) vs. visual control stimuli (false-fonts) and (2) sensitivity to orthographic familiarity, i.e. more efficient processing of familiar than unfamiliar visual word forms. Furthermore, we expected children with dyslexia to show impairments on both of these functional levels of VWF-system specialization. Finally, we aimed to clarify whether a potential dysfunction in children with dyslexia is *spatially* confined to the VWFA or extends over the full range of the VWF-system along the posterior-anterior axis of the occipitotemporal gyrus.

General aim 2 (Study B): To examine, by means of seed-voxel correlation mapping, functional connectivity in young children with dyslexia during a continuous phonological lexical processing task, focussing on the systematic variations of connectivity in the VWF-system.

Hypotheses: We investigated whether functional connections with left parietal and frontal language areas were specific for the VWFA or also existed for adjacent areas within the VWF-system in control children. In addition, we hypothesized that these possible functional connections are reduced in young children with dyslexia.

6. Study A

Children with Dyslexia lack Multiple Specializations along the Visual Word Form (VWF) System

Sanne van der Mark[1]*, Kerstin Bucher[1]*, Urs Maurer[2,3], Enrico Schulz[2,4], Silvia Brem[2,5], Jsabelle Buckelmüller[2], Martin Kronbichler[6,7], Thomas Loenneker[1,8], Peter Klaver[1], Ernst Martin[1,8], Daniel Brandeis[2,8]

* *The first and second authors contributed equally to this work.*

[1] *MR-Center, University Children's Hospital, University of Zurich, Zurich, Switzerland*

[2] *Department of Child and Adolescent Psychiatry, University of Zurich, Zurich, Switzerland*

[3] *Sackler Institute for Developmental Psychobiology, Weill Medical College of Cornell University, New York, USA*

[4] *Department of Neurology, Technische Universität München, (81675) München, Germany*

[5] *Agora Center, University of Jyväskylä, Jyväskylä, Finland*

[6] *Department of Psychology & Center for Neurocognitive Research, University of Salzburg, Salzburg, Austria*

[7] *Department of Neurology & Center for Neurocognitive Research, Christian Doppler Clinic, Paracelsus Private Medical University, Salzburg, Austria*

[8] *Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland*

Corresponding Author:

Daniel Brandeis, Department of Child and Adolescent Psychiatry, Brainmapping Research, Neumunsterallee 9, CH-8032 Zurich, Switzerland, phone: +41 43 499 2763, fax: +41 43 499 2604, E-mail: brandeis@kjpd.uzh.ch

Submitted to: NeuroImage.

6.1 Abstract

Developmental dyslexia has been associated with a dysfunction of a brain region in the left inferior occipitotemporal cortex, called the 'visual word-form area' (VWFA). In adult normal readers, the VWFA is specialized for print processing and sensitive to the orthographic familiarity of letter strings. However, it is still unclear whether these two levels of occipitotemporal specialization are affected in developmental dyslexia. Specifically, we investigated whether (a) these two levels of specialization are impaired in dyslexic children with only a few years of reading experience and (b) whether this impairment is confined to the left inferior occipitotemporal VWFA, or extends to adjacent regions of the 'VWF-system' with its posterior-anterior gradient of print specialization. Using fMRI, we measured brain activity in 18 dyslexic and 24 age-matched control children (age 9.7-12.5 years) while they indicated if visual stimuli (real words, pseudohomophones, pseudowords and false-fonts) sounded like a real word. Five adjacent regions of interest (ROIs) in the bilateral occipitotemporal cortex covered the full anterior-posterior extent of the VWF-system. We found that control and dyslexic children activated the same main areas within the reading network. However, a gradient of print specificity (higher anterior activity to letter strings but higher posterior activity to false-fonts) as well as a constant sensitivity to orthographic familiarity (higher activity for unfamiliar than familiar word-forms) along the VWF-system could only be detected in controls. In conclusion, analyzing responses and specialization profiles along the left VWF-system reveals that children with dyslexia show impaired specialization for both print and orthography.

6.2 Introduction

Developmental dyslexia is a severe, specific disorder of reading acquisition with a high prevalence and familial risk (Schulte-Körne 2001). Converging evidence from neuroimaging studies investigating dyslexia suggests functional deficits in brain regions involved in reading, including left inferior frontal gyrus, left parietotemporal cortex and left occipitotemporal gyrus (for a review see (Shaywitz and Shaywitz 2005)). Next to the well-documented phonological core deficit in dyslexia (Ramus, Rosen et al. 2003), another major deficit in individuals with dyslexia is the impaired automaticity of visual word processing, which prevents skilled, fluent (automatic) reading. While neuroimaging studies in normal-reading adults have identified a particular part of the left inferior occipitotemporal cortex, called the visual word-form area (VWFA, hereafter also referred to as "the VWFA proper"; Talairach coordinates: ± -43 -54 -12, with a standard deviation of ± 5 mm) (Cohen, Dehaene et al. 2000), as being specialized for visual word processing, studies in dyslexic readers implicate a dysfunction in this left inferior occipitotemporal region (for a review see Shaywitz and Shaywitz, 2005). More specifically, in normal-reading adults at least two levels of VWFA specialization have been proposed to exist: a fast, coarse form of visual tuning for print (letter strings vs. visual control stimuli) and specialization at the whole-word level, i.e. more efficient processing of familiar than unfamiliar word-forms, also called orthographic familiarity effect (Kronbichler, Bergmann et al. 2007; Bruno, Zumberge et al. 2008). However, functional magnetic resonance imaging (fMRI) studies examining visual tuning for print in the VWFA of healthy adults provide inconsistent results. While some studies found that words evoke stronger activation in the VWFA than visual control stimuli such as checkerboards (Cohen, Lehericy et al. 2002), false-fonts (Vinckier, Dehaene et al. 2007), or pictures (Gauthier, Tarr et al. 2000; Hasson, Levy et al. 2002), other studies found similar activation for both words and false-fonts (Tagamets, Novick et al. 2000; Brem, Bucher et al. 2006). The second level of VWFA specialization concerns orthographical familiarity with letter strings. In adults and adolescents, pseudohomophones (PH, phonologically familiar but

orthographically unfamiliar forms of real words) and pseudowords (PW, phonologically and orthographically unfamiliar word-forms without semantic content) were shown to evoke stronger activation than real words in the VWFA (Kronbichler, Bergmann et al. 2007; Bruno, Zumberge et al. 2008).

Furthermore, previous studies in healthy subjects demonstrated that visual tuning to words is not confined to the VWFA. Rather, a posterior-to-anterior gradient of increasing print specificity was found in a left occipitotemporal network (VWF-system) in adults (Brem, Bucher et al. 2006; Vinckier, Dehaene et al. 2007) and adolescents (Brem, Bucher et al. 2006). Similarly, effective connectivity with prefrontal activity during the reading of regular words, exception words, and pseudo-words showed selective increase with distinct occipitotemporal areas (posterior, middle, anterior fusiform), depending on word-type (Mechelli, Crinion et al. 2005). A priming study of Dehaene et al. (2004) demonstrated that posterior but not anterior fusiform regions are sensitive to small changes in letter position, suggesting that binding of letters into words is accomplished by a posterior-to-anterior gradient of increasingly invariant processing of letters in the left occipitotemporal cortex (Dehaene, Jobert et al. 2004). However, since most previous studies examining dyslexia focused on the VWFA proper, it remains to be determined whether dyslexia-related impairments in visual word-form processing are limited to the VWFA proper or whether such a dysfunction affects the occipitotemporal VWF-system and its gradients of specialization. Therefore, VWF-system gradients for both print and orthography were investigated in the present study.

Several studies on visual word processing in dyslexic readers implicate a dysfunction in the left inferior occipitotemporal cortex. Recently, it was demonstrated that dyslexic adults and adolescents did not show the orthographic familiarity effect in the VWFA (Wimmer, Kronbichler et al. personal communication) characterizing nonimpaired readers (Kronbichler, Bergmann et al. 2007; Bruno, Zumberge et al. 2008). Moreover, functional neuroimaging studies investigating dyslexia found the VWFA to be generally underactivated during word reading in adults and adolescents (Salmelin, Service et al. 1996; Rumsey, Horwitz et al. 1997; Rumsey, Nace et al. 1997; Brunswick, McCrory et al. 1999; Helenius, Tarkiainen et al. 1999; Paulesu,

Demonet et al. 2001; Shaywitz, Shaywitz et al. 2003; McCrory, Mechelli et al. 2005; Wimmer, Kronbichler et al. personal communication) as well as in children (Shaywitz, Shaywitz et al. 2002; Cao, Bitan et al. 2006; Maurer, Brem et al. 2007; Shaywitz, Skudlarski et al. 2007). It is important to note that most of these previous studies found a *general* underactivation in the VWFA, rather than a *specific* impairment of the two levels of specialization (i.e. more efficient processing of one stimulus type versus another). Such a general underactivation was commonly identified by contrasting e.g. words or pseudowords with a low-level baseline consisting of crosshair fixation (Rumsey, Horwitz et al. 1997; Rumsey, Nace et al. 1997; Cao, Bitan et al. 2006; Wimmer, Kronbichler et al. personal communication), symbol strings (Helenius, Tarkiainen et al. 1999; Maurer, Brem et al. 2007), a line judgment task (Shaywitz, Shaywitz et al. 2002; Shaywitz, Shaywitz et al. 2003), or rest with eyes closed (Brunswick, McCrory et al. 1999). So far, a single study reported reduced left occipitotemporal activation in dyslexics vs. controls for the comparison of words with a high-level baseline consisting of false-fonts (McCrory, Mechelli et al. 2005). Finally, no study so far has compared both levels of word processing in young normal-reading and dyslexic children in a systematic manner. Thus, it still remains to be seen whether dyslexia-related impairments in visual word-form processing affect the VWF-system and its gradients of specialization in dyslexic children with only a few years of reading experience.

The aim of this study was to test the hypothesis that a dysfunction of specialization within the VWF-system for processing both print and orthographic familiarity is already present in young children with dyslexia. We used fMRI to examine the activation gradients along the bilateral occipitotemporal cortices of control and dyslexic children. The participants performed a phonological lexical decision task ("Does it sound like a real word?") including four types of letter strings varying in orthographic familiarity, i.e. real words (familiar word-forms; e.g., Taxi), pseudohomophones and pseudowords (unfamiliar word-forms; e.g., Taksi and Tazi, resp.), and false-fonts (visual control stimuli). We expected control children to show a dissociation of two *functional* levels of specialization within the VWF-system: (1) coarse specialization for print, i.e. differential

processing of letter strings (real words, pseudohomophones and pseudowords) vs. visual control stimuli (false-fonts) and (2) sensitivity to orthographic familiarity, i.e. more efficient processing of familiar than unfamiliar visual word-forms. Furthermore, we expected children with dyslexia to show impairments on both of these functional levels of VWF-system specialization. Finally, we aimed to clarify whether a potential dysfunction in children with developmental dyslexia is *spatially* confined to specific regions or extends over the full range of the VWF-system along the posterior-anterior axis of the occipitotemporal gyrus.

6.3 Materials and Methods

6.3.1 Participants

The 42 children (mean age 11.3 yrs, ±0.6yrs) who participated in this study were grouped according to their reading scores (see Table 6.1): 18 children with dyslexia and 24 control children. Twenty-six children were part of an extensive longitudinal study investigating developmental dyslexia in children (Maurer, Bucher et al. 2003; Maurer, Brem et al. 2007; Schulz, Maurer et al. 2008) and 16 children participated only in either 4th or 5th grade. Eight additional children were excluded from analysis: 1 child due to head movement exceeding the a-priori maximum movement criterion (> ±2 mm translation or > ±2° rotation), 7 children because of poor performance (accuracy < 60% in one or more conditions) in the phonological lexical decision task (n = 5) or in the orthographical task (n = 2).

The children were screened for a history of neurological diseases or psychiatric disorders and reported all normal or corrected-to-normal vision. Children from families with a foreign language background (i.e. both parents' first language was not (Swiss-) German) were excluded from the study. The children were contacted by distributing handouts at schools. The children and their parents/caretakers gave their informed written consent to participate in the study. The study was approved by the local ethical committee.

Subjects were submitted to a typical test battery for German dyslexia (Wimmer 1996; Mayringer and Wimmer 2000; Wimmer, Mayringer et al. 2000; Wimmer 2006) using the correct word-per-minute reading score as a reading fluency measure, which is the core criterion for diagnosing dyslexia in readers of the regular German orthography (Wimmer, Mayringer et al. 2000). The children tested in the 4th grade (n = 6), were grouped based on their "correct words per minute" reading score of the Salzburg Reading and Spelling Test ("Salzburger Lese- und Rechtschreibtest" (SLRT) (Landerl, Wimmer et al. 1997)), a test designed to assess dyslexia in children in 2nd to 4th grade. Reading skills of the children tested in 5th grade (n = 36) were assessed with the "Ein-Minuten Leseflüssigkeitstest" (Landerl and Willburger in press), which required the children to accurately read as many words as possible from a list within 1 minute. The "correct words per minute" score of the 4th graders was compared to the published SLRT norms (Landerl et al., 1997), the "correct words per minute" score of the 5th graders was compared to the distribution in a normative group of 56 children, as detailed in (Schulz, Maurer et al. 2008). All children from the present fMRI study were categorized as dyslexic if their "correct words per minute"-score was below the 10th percentile of the corresponding norms, and as control children if their score was equal to or above the 20th percentile of the norms. As can be seen in Table 6.1, the children with dyslexia performed worse not only on word reading (the criterion for grouping), but also on pseudoword reading.

Nonverbal and verbal intelligence was estimated using the block design and the similarities subtest of the HAWIK-III intelligence test (Tewes, Rossmann et al. 2000). The groups were matched for gender, age, and handedness. Furthermore, estimated verbal IQ did not differ between the groups and particularly non-verbal IQ was well-matched, as expected (Table 6.1). In addition, all parents filled out a questionnaire regarding the child's handedness (Edinburgh Handedness Inventory (Oldfield 1971)). Finally, spelling scores consist of the mean % correctly written words of pooled SLRT scores of the 4th graders and DRT-5 scores (Diagnostischer Rechtschreibtest (Grund, Haug et al. 1995)) of the 5th graders.

Table 6.1. Demographic Characteristics of the Control and Dyslexic Children and Group Differences (*t*-test or chi-square).

	Dyslexic Children	Control Children	*P*-value
n	18	24	–
Age (years)	11.4 ± 0.7	11.3 ± 0.4	n.s.
Sex (male:female)	10:8	10:14	n.s.
Handedness (right:left)	15:3	17:7	n.s.
Estimated Verbal IQ	109 ± 11	114 ± 14	n.s.
Estimated Non-verbal IQ	111 ± 12	112 ± 11	n.s.
Correctly read W/min	49 ± 8	93 ± 16	$P < .001$
Correctly read PW/min	32 ± 5	54 ± 14	$P < .001$
Spelling	30 ± 23	86 ± 21	$P < .001$

Means and standard deviations (SD) are displayed; n.s.: non-significant.

6.3.2 Stimuli and Task

During fMRI acquisition, participants performed a phonological lexical decision task in which they had to decide if a visually presented stimulus sounded like a real word or not (Kronbichler, Bergmann et al. 2007). The 176 stimuli consisted of 44 orthographically familiar forms of German nouns (W), 44 pseudohomophones (PH; phonologically correct but orthographically unfamiliar forms of the same words), 44 pseudowords (PW; phonologically and orthographically unfamiliar forms) and 44 false-fonts (FF). Additionally, 65 null events (fixation cross only) were presented. The stimuli were presented in a pseudo-randomized fashion, and the order of the stimuli was the same for all participants.

The letter string stimuli (W, PH, PW) used were the same as in the study of Kronbichler et al. (Kronbichler, Bergmann et al. 2007) with minor

adaptations because the children in our study speak a different German dialect (Swiss-German). However, an essential difference from the task of Kronbichler et al. is that we added false-font (FF) strings as non-lexical control stimuli. For each letter, upper and lower case, a FF character was created. In contrast to previous studies (Kronbichler, Bergmann et al. 2007; Bruno, Zumberge et al. 2008), there were just as many trials requiring a "yes" response as a "no" response, due to the inclusion of the FF items. This excluded the possibility of a response bias toward "yes" responses. The characteristics of the four item types are shown in detail in Table 6.2 and a complete listing of all stimuli used can be found in Supplementary Table 6.1 online. All stimuli were matched for complexity, character size, and number of characters in a string (3-6 characters; average horizontal visual angle: 2.2°, range: 1.3-3°). In addition, the letter string types were matched for bigram frequency.

In the event-related design, the stimuli were presented for 700 ms with an interstimulus interval (ISI) of 2550 ms during which a fixation cross was shown. Participants were instructed to press 'Yes' for W (e.g. Taxi) and PH (e.g. Taksi) and to press 'No' for PW (e.g. Tazi) and FF. For responding, they used the index finger and middle finger of their dominant hand. Yes- and No-Buttons were counterbalanced across participants and groups. Responses were made via a fiber-optics response button box (Lumina LP-400, **Cedrus Corporation**, San Pedro, USA) and stimulus delivery and response registration was controlled by Presentation (Neurobehavioral Systems Inc., Albany, CA, USA). To become familiar with the task, the subjects were given a short practice version (with different stimuli) of the task outside the scanner. In addition to the fMRI session, the participants also performed the task during an ERP session, of which the results are not further discussed here. The order of the ERP and fMRI session was counterbalanced across subjects and groups.

A separate orthographic judgment task (i.e., "Is this a correctly spelled word?"), which included the W-, PH- and PW-items of the experimental task but no FF stimuli, determined the participants' ability to differentiate the familiar (W) from the unfamiliar, misspelled, forms of the same words (PH).

This task was self-paced and was performed immediately after MRI acquisition.

6.3.3 fMRI Acquisition

MRI data was acquired on a 3.0 T (GE Healthcare) whole-body scanner. For functional imaging, 535 functional images sensitive to BOLD contrast with 25 axial slices covering the whole brain were acquired with a T2*-sensitive multi-slice echo planar imaging (EPI) sequence (TR = 1.5s; TE = 31ms; FOV = 24cm; image matrix = 64 x 64; voxel size = 3.75 x 3.75 x 5 mm^3; flip angle = 50°). The first 4 scans were discarded to allow for equilibration effects. Participants were fitted with earplugs and viewed the stimuli via TFT video goggles (Resonance Technology Inc., California, USA). Particular care was taken to stabilize the children by using vacuum cushions and custom made padding.

6.3.4 Region of Interest Analyses

Five non-overlapping regions of interest (ROIs; spheres with a 5mm radius) were defined (Figure 6.3), covering the putative VWFA of the fusiform gyrus (Cohen, Dehaene et al. 2000) and neighbouring areas along a posterior-anterior axes in the left hemisphere, following the slight anterior decline of the temporal lobe. The ROI coordinates were based on those of Brem et al. (2006): ROI1 (MNI coordinates (x/y/z): -42, -34, -20), ROI2 (-42, -44, -18), ROI3 (VWFA proper; -42, -54, -17), ROI4 (-42, -64, -16), and ROI5 (-42, -74, -14). The mean percent signal change values in these ROIs were computed using the MARSBAR toolbox in SPM5 (http://marsbar.sourceforge.net/) (Brett, Anton et al. 2002) on unsmoothed data.

6.3.5 Statistical Analyses

The behavioural data of both the experimental and the orthographic judgment task, response accuracy and reaction times (correct trials only) were analyzed separately in a repeated measures analysis of variance (ANOVA) with the within-subject factor 'condition' (W, PH, PW, FF) and between subject factor 'group' (dyslexics and controls) (Table 6.2). Statistical analyses were performed using SPSS software (SPSS Inc., Chicago, USA).

Functional MRI data preprocessing and statistical analysis was done using SPM5 (Wellcome Department of Imaging Neuroscience, London, http://www.fil.ion.ucl.ac.uk/spm). The data were first motion corrected and the images were then normalized using a 4th Degree B-Spline interpolation method to match the Montreal Neurological Institute (MNI) EPI template. Finally, functional volumes were resampled to isotropic 3 mm^3 voxels and spatially smoothed with a 9 mm full width at half maximum isotropic Gaussian kernel.

Statistical analysis of the fMRI data was performed in a two stage mixed effects model. In the subject-specific first level model, the event-related activation evoked by each trial type (W, PH, PW, FF) was modelled using the standard SPM hemodynamic response function with its temporal derivative. To control for performance-related confounds, only correct trials were used in the statistical analysis. Correct and incorrect responses were modelled separately in the design matrix and a covariate of no interest was entered. The data were temporally high-pass filtered with a frequency cut-off period of 128s, and serial correlations were accounted for using an autoregressive model of the first order. Condition and group analyses were conducted with second-level random-effect *t*-tests using the individual contrast images. Statistical parametric maps of *t* values were generated. One-sample *t*-tests across all participants in each group were performed to determine whether activation within a group was significant. Clusters (k > 10) including voxels exceeding a false discovery rate (FDR) corrected $P < .05$ were considered to show significant activations (Genovese, Lazar et al. 2002). Paired *t*-tests were performed to determine whether there were reliable differences between conditions. Words were contrasted with false-fonts (W vs. FF) to investigate visual specialization for print vs. visual control stimuli. Furthermore, pseudohomophones were contrasted with words (PH vs. W) and pseudowords with words (PW vs. W), both reflecting the orthographic familiarity effect, i.e., more activity for orthographically unfamiliar than for familiar letter strings. In addition, two-sample *t*-tests (control vs. dyslexic children) were computed to determine whether there were reliable group differences. For paired and two-sample *t*-tests, a $P < .001$ uncorrected for multiple comparisons and a cluster size k > 10 were used to determine

significantly activated areas. While our threshold of uncorrected p < .001 may seem liberal at first, it is in fact comparable to (Cao, Bitan et al. 2006; Booth, Bebko et al. 2007; Hoeft, Meyler et al. 2007; Wimmer, Kronbichler et al. personal communication) or better (Brambati, Termine et al. 2006; Kronbichler, Hutzler et al. 2006) than most of the previous fMRI papers reporting effects in the VWFA in dyslexia. Activated brain structures were identified by transforming the MNI coordinate system into the standard brain atlas of Talairach and Tournoux (Talairach and Tournoux 1988), using mni2tal.m (provided by Matthew Brett; http://www.mrccbu.cam.ac.uk/Imaging/Common/mnispace.shtml).

For the ROI analysis of the fMRI data, a repeated measures ANOVA with the within-subject factors 'condition' (W, PH, PW, FF), 'ROI' (ROI 1, 2, 3, 4, 5), and between subject factor 'group' (dyslexics and controls) was computed. Next, separate ANOVAs were computed to contrast specific conditions, i.e., for W and FF, PW and FF, mean(W, PH, PW) and FF, PH and W, and finally PW and W. Although averaging the three letter string conditions for comparison to FF eliminates the different mean levels, this average accurately captures the difference in gradients (e.g., slopes or profiles over ROIs) between letter strings and FF. In an ANOVA including only the letter string conditions but excluding the false-fonts, the interaction of ROI*condition*group was no longer significant. The post-hoc tests used to follow up significant ANOVA effects are reported using the uncorrected P < .05 threshold; adjusting for multiple testing of the 5 ROIs would have required P < .01.

6.4 Results

6.4.1 Behavioural Results

Reaction time, accuracy and *p*-values of group comparisons for the phonological lexical decision task and the orthographical judgment task are reported in Table 6.2. In the phonological lexical decision task performed inside the scanner, accuracy scores differed significantly between conditions

($F(3,38) = 74.60$, $P < .001$) and groups ($F(1,40) = 13.68$, $P = .001$). In addition, an interaction of condition with group was found ($F(3,38) = 9.83$, $P < .001$). Post-hoc *t*-tests revealed that children with dyslexia made significantly more mistakes than control children for PH (more erroneous "no" responses) and for PW (more erroneous "yes" responses), whereas the groups performed equally well for W and FF.

Analysis of the reaction times yielded significant main effects of condition ($F(3,38) = 170.22$, $P < .001$) and group ($F(1,40) = 17.05$, $P < .001$) in addition to an interaction of condition with group ($F(3,38) = 21.09$, $P < .001$). Post-hoc *t*-tests revealed that the children with dyslexia responded more slowly than the control children to all three letter string conditions. Note that there was no significant group difference for FF.

Performance on the orthographic judgment task (i.e., "Is this a correctly spelled word?") outside the scanner, revealed an accuracy difference between conditions ($F(2,39) = 38.42$, $P < .001$), and a highly significant condition by group interaction ($F(2,39) = 13.30$, $P < .001$). Post-hoc *t*-tests revealed that dyslexics made more mistakes than control participants for PH.

6.4.2 fMRI Results

Conditions Contrasted Against Fixation

Contrasts of each separate condition against fixation are shown in Figure 6.1. A detailed listing of the activation clusters is provided in Supplementary Table 6.2 online. As expected, all three letter string conditions activated predominantly left hemispheric language regions in both controls and dyslexic readers. False-fonts evoked mostly activation in bilateral occipital and left parietal areas in control children but no significant activation in the children with dyslexia at the current threshold. However, when the threshold was lowered to $P < .05$ uncorrected, similar regions were found to be active in the children with dyslexia and the control children.

Comparing the control vs. dyslexic children for W and FF vs. fixation revealed no significant group differences. For PH vs. fixation, control children showed more activation than the children with dyslexia in the bilateral frontal lobe, parietal lobule and insula as well as the left fusiform gyrus. For PW vs. fixation, controls showed more activation than dyslexics in left inferior parietal lobule.

Table 6.2. Performance During Phonological Lexical Decision Task and Item Characteristics.

Measures	Words	Pseudo-homophones	Pseudowords	False-Fonts
Task Performance				
Phonological lexical decision task (fMRI)				
Accuracy (%)				
Control children	94 (±7)	87 (±9)	91 (±8)	99 (±1)
Dyslexic Children	92 (±8)	80 (±9)	78 (±7)	98 (±3)
p-value	n.s.	*P* = .017	*P* < .001	n.s.
Reaction time (ms)				
Control children	1033 (±299)	1196 (±340)	1338 (±361)	837 (±227)
Dyslexic Children	1401 (±297)	1608 (±252)	1904 (±288)	895 (±198)
p-value	*P* < .001	*P* < .001	*P* < .001	n.s.
Orthographical judgment task				
Accuracy (%)				
Control children	93 (±19)	90 (±19)	95 (±20)	-
Dyslexic Children	90 (±5)	77 (±11)	96 (±4)	-
p-value	n.s.	*P* = .013	n.s.	-
Item Characteristics				
Number of characters	4.5 (± 0.7)	4.5 (± 0.8)	4.5 (± 1.0)	4.5 (± 0.7)
Bigram Frequency	11771 (± 8385)	10282 (± 9043)	11328 (± 9094)	-
Word Frequency	68.3 (± 74.2)	-	-	-

Means and standard deviations (SD) are displayed for the control, the dyslexic children and all four item types. Significant *p*-values indicate group differences; n.s.: non-significant.

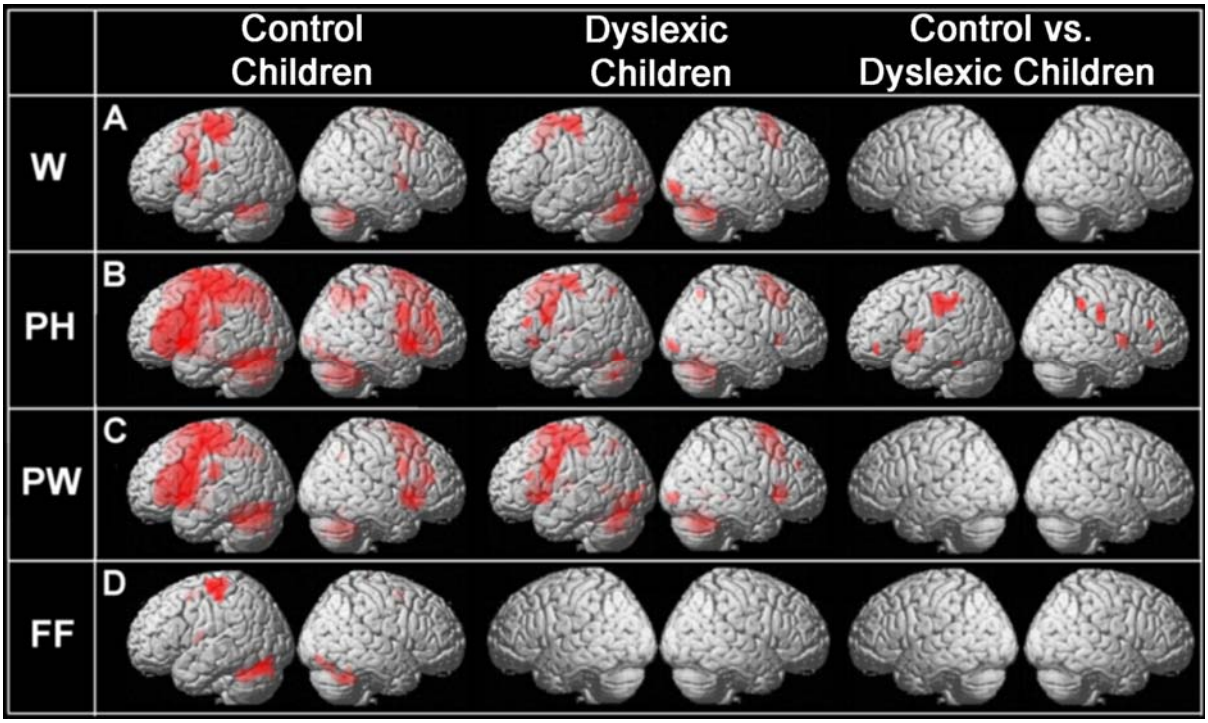


Figure 6.1. Activations Induced in the Left and Right Occipitotemporal Cortex and in the Whole Brain by Letter Strings and False-Fonts in Both Controls and Children with Dyslexia, Overlaid on a Surface-Rendered Single Subject Brain Normalized to MNI Template. Comparison of BOLD activation evoked by each condition (W, PH, PW, FF) against fixation in (A) control and (B) dyslexic children (FDR corrected, $P < .05$, $k > 10$. (C) Comparison of BOLD activation for control vs. dyslexic children ($P < .001$ uncorrected for multiple comparisons, $k > 10$). Abbreviations: W: words, PH: pseudohomophones, PW: pseudowords, FF: false-fonts.

Next, Figure 6.2 and Table 6.3 show the results of the main contrasts for each group separately. A detailed listing of the results of the comparison of FF, PH and PW with the orthographically familiar W for each group separately as well as the comparison between groups is provided in Supplementary Table 6.2-6.4 online.

Comparison of Words with Visual Control Stimuli

The contrast W vs. FF in control readers revealed bilateral activation in the frontal lobe as well as in the left insula. When the threshold was lowered to $P < .005$ uncorrected, stronger activation for W than FF was detected in left anterior fusiform gyrus (MNI coordinates: x = -48, y = -45, z = -21) in

controls (Figure 6.4). The opposite contrast (FF vs. W) showed activation maxima in left posterior fusiform gyrus and bilateral occipital gyrus. In children with dyslexia, W evoked stronger activation than FF in the bilateral frontal cortex and the right lingual gyrus, and FF evoked stronger activation than W in right inferior parietal lobule. Finally, control children showed stronger activation than dyslexic children in left inferior and middle occipital gyrus, bilateral posterior cingulate gyrus and the left hemispheric cuneus for the contrast FF vs. W. The group comparison for W vs. FF showed no significant voxels.

Comparison of Unfamiliar with Familiar Word-Forms

For the contrast PH vs. W, the controls demonstrated stronger activation for PH in left superior parietal lobule, left inferior frontal region, the left precuneus, the left fusiform gyrus, the right insula and in bilateral frontal and parietal areas. No region showed higher activation for W than for PH. In the children with dyslexia, the left and right frontal and parietal cortex were activated more for PH than for W. The cortical activations for the opposite contrast W vs. PH in dyslexic children included the left frontal cortex, and the right hemispheric temporal gyrus, precuneus and angular gyrus. For the group comparison, we found that the contrast PH vs. W showed more activation in the control than the dyslexic children in the left parietal, temporal cortex, and the left insula. No differences between groups were found for the contrast W vs. PH.

The contrast of PW with W in controls yielded activations comparable to the contrast PH vs. W, with complementary activity in the left temporal and right frontal cortex. The opposite contrast (W vs. PW) indicated activation in the left hemispheric frontal cortex, parietal lobe, insula, bilateral cingulate gyrus and right angular gyrus. In children with dyslexia, the contrast PW vs. W yielded slightly stronger activation than PH vs. W. Activated regions included the left hemispheric precentral cortex, left occipital and frontal lobe and right hemispheric cingulate gyrus. The opposite contrast W vs. PW yielded activations similar to W vs. PH, with additional activity in the left hemispheric frontal and angular gyrus, the left precuneus as well as the right hemispheric parietal lobule and bilateral

cingulate gyrus. Finally, the contrasts PW vs. W and W vs. PW did not distinguish the groups.

Table 6.3. Main Activation Peaks of the Reading Network in Both Control and Dyslexic Children for Each Main Comparison of the Conditions.

Contrast	Group	Region	MNI Coordinates			*Z*
			x	*y*	*z*	
W > FF	Controls	L Inferior Frontal g.	-39	21	6	5.04
		L Insula	-48	9	3	4.63
		R Inferior Frontal g.	33	27	3	3.43
	Dyslexics	L Inferior Frontal g.	-51	27	18	4.42
		R Inferior Frontal g.	39	24	-3	3.66
PH > W	Controls	L Superior Parietal g.	-33	-51	51	5.25
		L Inferior Frontal g.	-30	20	2	4.79
		L Fusiform g.	-48	-60	-24	4.12
	Dyslexics	L Inferior Frontal g.	-39	6	30	4.60
PW > W	Controls	L Inferior Frontal g.	-51	12	21	5.08
		L Fusiform g.	-42	-42	-21	3.51
	Dyslexics	L Inferior Frontal g.	-48	12	21	5.44
		L Middle Occipital g.	-36	-87	3	3.22

MNI coordinates (*x/y/z*) are listed for local maxima of significant clusters ($P < 0.001$, uncorrected for multiple comparisons). *Z*-values are listed for voxels at the local maxima. Abbreviations: W: words, PH: pseudohomophones, PW: pseudowords, FF: false-fonts, L: left hemisphere, R: right hemisphere, g.: gyrus.

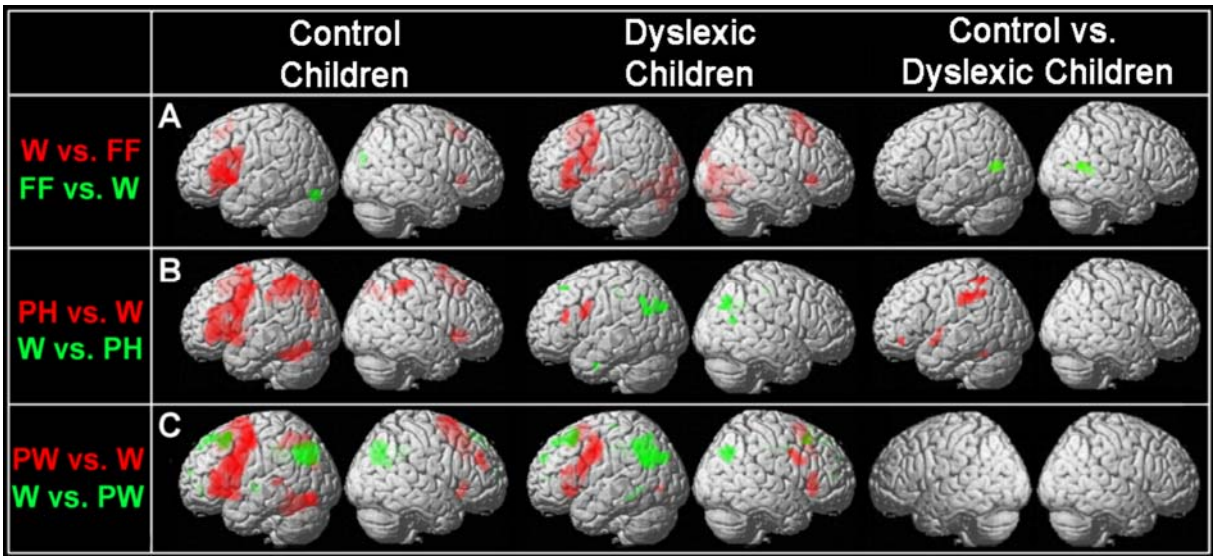


Figure 6.2. Activations Induced in the Left and Right Occipitotemporal Cortex and in the Whole Brain, Revealed by Contrasting the Main Conditions in Both Controls and Children with Dyslexia, Overlaid on a Surface-Rendered Single Subject Brain Normalized to MNI Template. BOLD activation evoked by the comparison of the letter string conditions (A) 'W vs. FF', 'FF vs. W', (B) 'PH vs. W', 'W vs. PH' and (C) 'PW vs. W', and 'W vs. PW' in control and dyslexic children. Regions of BOLD activation evoked by the group comparison 'controls vs. dyslexics' for the contrasts 'FF vs. W', 'PH vs. W', and 'PW vs. W'. Statistical threshold was $P < .001$ uncorrected for multiple comparisons, $k = 10$. Abbreviations: W: words, PH: pseudohomophones, PW: pseudowords, FF: false-fonts.

Visual Word form System

Brain responses were further investigated in five regions of interest in the left and right occipitotemporal cortex (Figure 6.3). Gradient images illustrating the spatial layout of the sensitivity of the occipitotemporal cortex are displayed in Figure 6.4. Since we were most interested in the effect of condition on left occipitotemporal activation in each group of children, we will focus on the three-way interaction of condition with ROI and group. For a complete listing of the effects and corresponding statistical values see Table 4. A repeated measures ANOVA including all four conditions revealed that the conditions produced different activation patterns in each ROI and group (interactions of condition*group and condition*ROI*group). Next, to examine the two levels of specialization for print independently, we computed three separate ANOVAs each including two conditions only, comparing the four conditions with each other.

Firstly, in order to test the VWF-system specialization for print, we compared words with visual control stimuli by computing an ANOVA with W and FF. This analysis yielded a significant interaction of condition*ROI*group ($F(4,37) = 3.1$, $P = .032$), indicating that the difference between W and FF is dependent on the location of the ROIs and group. Post-hoc *t*-tests confirmed that in the control children W produced less activation than FF in the most posterior ROI (ROI5: $t = -2.5$, $P = .021$), that W produced more activation than FF in the anterior ROI2 ($t = 2.5$, $P = .020$). By contrast, the dyslexic children showed a significant difference between W and FF only in the most anterior ROI (ROI1: $t = 2.3$, $P = .032$). Next, in order to clarify whether this gradient was specific to words or generalized to print, we calculated additional ANOVAs to contrast the conditions PW and FF (excluding semantic and lexical influences as confounding factors), as well as the mean of all letter string conditions (W, PH, PW) and FF (i.e., print vs. visual control stimuli). Both ANOVAs yielded a significant interaction of condition*ROI*group (PW and FF: $F(4,37) = 3.8$, $P = .007$; mean(W, PH, PW) and FF: $F(4,37) = 4.6$, $P = .003$). Post-hoc t-tests confirmed that, in controls, print evoked stronger activity than FF in all ROIs except the most posterior one (for PW vs. FF: ROIs 1 & 3 $P < .05$ and $t > 2.3$, ROI2 $P < .001$ and $t = 4.2$, except ROI4 $P < .1$ and $t = 2.0$, ROI5, n.s.; and similar for mean(W, PH, PW) vs. FF). By contrast, the dyslexic children did not show a significant difference between print and FF in any of the ROIs, except for ROI1 (for mean(W, PH, PW) vs. FF: $t = 3.0$, $P = .009$). These findings provide clear evidence that a posterior-to-anterior gradient of increasing coarse print specificity is disturbed in children with dyslexia.

Secondly, in order to examine the effect of orthographic familiarity on VWF-system activation, we compared the conditions W and PH as well as W and PW. The ANOVA for W and PH revealed a significant interaction of condition*group ($F(1,40) = 5.4$, $P = .025$). Post-hoc *t*-tests clarified that PH evoked significantly more activation than W in all 5 ROIs for the control children (Figure 6.3-6.4) (all ROIs $P < .01$ and $t > 3.0$). Conversely, the dyslexic children showed no difference between PH and W in most of the ROIs, except for ROI4 ($t = -2.5$, $P = .024$). In addition, the ANOVA with W and PW showed an interaction of ROI with group ($F(4,37) = 3.3$, $P = .021$), and *t*-

tests comparing PW and W in control children revealed significantly stronger activation for PW than W in ROIs 2-5 (ROI2 $P < .01$ and $t = 3.2$; ROI 3-5 $P < .05$ and $t > 2.6$) and a trend in ROI1 ($t = 1.8$, $P = .089$). Again, the children with dyslexia showed no difference between PW and W in any of the ROIs, except for ROI1 ($t = 2.4$, $P = .027$). Furthermore, the VWF-system of control children was activated more for PH than for PW in ROI4 ($t = 2.4$, $P = .026$) and ROI3 ($t = 2.1$, $P = .048$), in contrast to that of the dyslexic children (all $P > .1$).

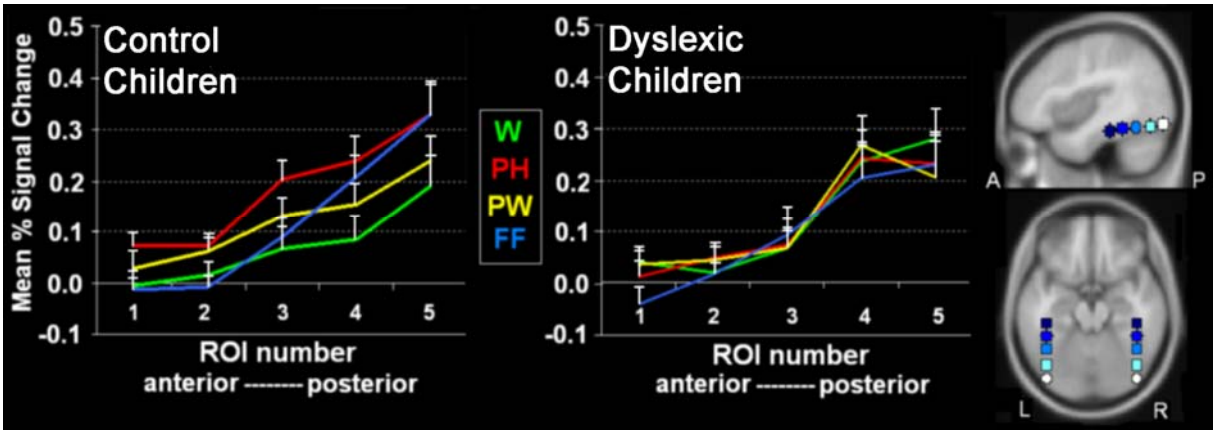


Figure 6.3. ROI Analysis in the VWF-System. BOLD response (mean percent signal change) in five consecutive regions of interest along the anterior-posterior axis of the left occipitotemporal cortex. Error bars represent 1 S.E.M. across subjects.

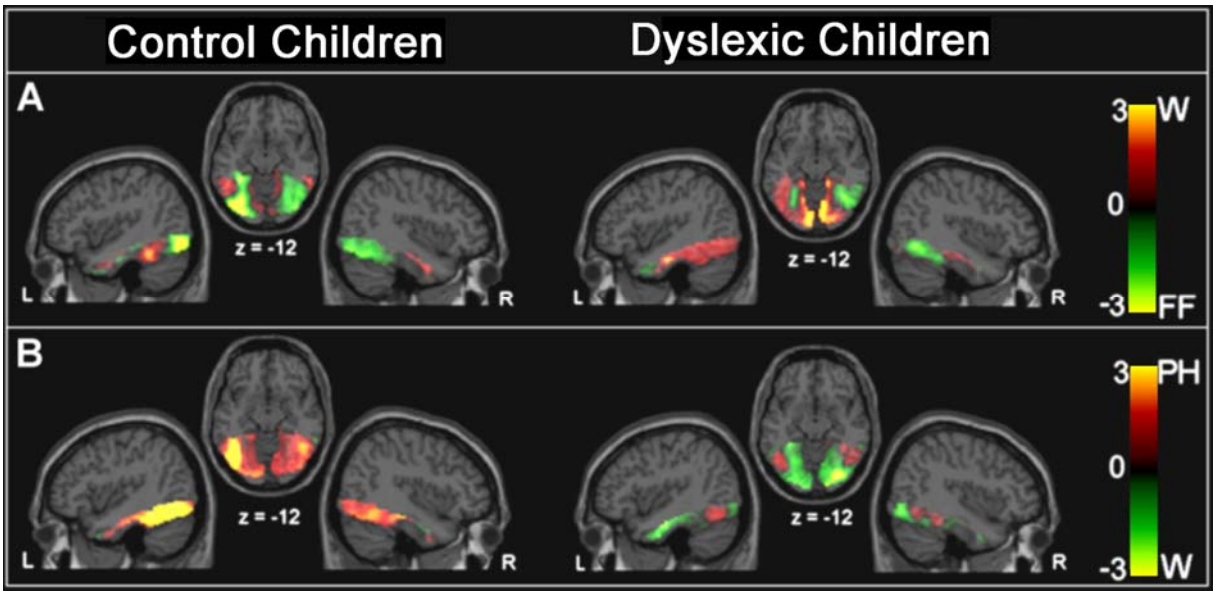


Figure 6.4. Gradient Images Illustrating the Spatial Layout of Occipitotemporal Cortex Sensitivity for Print. Occipitotemporal sensitivity to W vs. FF (A) and W vs. PH (B) is

shown. Activation maps are displayed on left (x = -42) and right (x = 42) hemispheric slices (colour bar indicates T-values with range -3 to 3) and are restricted to occipitotemporal areas (including the fusiform gyrus, calcarine fissure, occipital inferior and lingual gyrus; mask generated by Pickatlas software version 2.3 (Maldjian, Laurienti et al. 2003)).

Table 6.4: ROI Analysis.

	A		**B**		**C**		**D**	
ANOVA:	**W, PH, PW and FF**		**W and FF**		**W and PH**		**W and PW**	
ROI	$F(4,37) = 12.18$	$P < .001$	$F(4,37) = 10.93$	$P < .001$	$F(4,37) = 9.31$	$P < .001$	$F(4,37) = 8.11$	$P < .001$
ROI * group	$F(4,37) = 2.26$	$P = .087$	–	–	$F(4,37) = 3.26$	$P = .023$	$F(4,37) = 3.29$	$P = .021$
condition	$F(3,38) = 12.20$	$P < .001$	–	–	$F(1,40) = 18.61$	$P < .001$	$F(1,40) = 16.50$	$P < .001$
condition * group	–	–	–	–	$F(1,40) = 5.40$	$P = .025$	–	–
ROI * condition	$F(3,38) = 2.07$	$P = .045$	$F(1,40) = 2.40$	$P = .072$	$F(4,37) = 2.96$	$P = .039$	–	–
ROI * condition * group	$F(12,29) = 2.16$	$P = .036$	$F(4,37) = 3.05$	$P = .032$	–	–	–	–
group	–	–	–	–	–	–	–	–

A) Repeated Measures Analysis of Variance (RM-ANOVA): 2 hemispheres * 4 conditions * 5 ROIs * 2 groups; B),C),D) RM-ANOVA: 2 hemispheres * 2 conditions * 5 ROIs * 2 groups. Abbreviations: W: words, PH: pseudohomophones, PW: pseudowords, FF: false-fonts, hem: hemisphere, cond: condition, gr: group.

6.5 Discussion

The present fMRI study compared visual word processing in control children and in children with dyslexia, focussing on gradients of brain activation in the occipitotemporal VWF-system. The children with dyslexia exhibited typically poor reading performance. The behavioural results indicated that these children had problems not only with phonological decoding (phonological lexical decision task) but also with distinguishing between orthographically correctly and incorrectly written words (orthographic judgement task).

The fMRI data showed that we were able to demonstrate in a single experiment (thus controlling for general arousal levels) that reading related activity in the VWF-system can be dissociated at (at least) two functional levels in young children – i.e. print specificity and orthographic familiarity Most importantly, the data provide two core findings supporting our main hypothesis that impaired specialization for print and automatization of word reading exists early in reading acquisition in dyslexic children and is linked to a dysfunctional VWF-system. First, we found that the posterior-to-anterior gradient of increasing print specificity, as identified in control children by contrasting letter strings (W, PH and PW) with visual control stimuli (FF), was not detectable in dyslexic readers. Second, we found that dyslexic children did not show the orthographic familiarity effect on occipitotemporal activation (i.e., higher activity for unfamiliar than for familiar word-forms) anywhere in the VWF-system. These two core findings demonstrate that word processing deficits in dyslexic children are associated with an early impairment of two types of specialization for visual word processing subserved by the left occipitotemporal VWF-system.

Absence of Posterior-to-Anterior Gradient of Increasing Print Specificity in Dyslexic Children

Our findings for control children are consistent with previous fMRI studies in adults and adolescents since we demonstrated that FF evoked stronger activation than W in left posterior occipitotemporal cortex (Brem, Bucher et al. 2006) and W evoked stronger activity than FF in left anterior

occipitotemporal cortex (Brem, Bucher et al. 2006; Vinckier, Dehaene et al. 2007), whereas W and FF evoked similar activity in the central ROI (VWFA proper) (Price, Wise et al. 1996; Tagamets, Novick et al. 2000; Turkeltaub, Gareau et al. 2003; Brem, Bucher et al. 2006). This result demonstrates that, while visual control stimuli are processed more efficiently than words in posterior regions, this preference is reversed (i.e. stronger activation for words than false fonts) in increasingly more anterior locations. These findings provide support for a posterior-to-anterior gradient of increasing specificity for words. As a novel finding, we were able to demonstrate that this gradient was not limited to words (versus FF) but generalized to other letter strings. Specifically, not only the comparison of W vs. FF but also of PW vs. FF and the mean of all letter string types (W, PH, PW) vs. FF showed increasing specificity for print vs. false-fonts from posterior towards anterior regions in control children (interaction condition*ROI*group). In the following, we will therefore refer to this gradient as the posterior-to-anterior gradient of increasing print specificity.

In contrast to control children, dyslexic children did not show differential activation for letter strings (W, PH and PW) and visual control stimuli (FF) in the VWF-system, indicating that the posterior-to-anterior gradient is absent in dyslexics. This finding is consistent with earlier studies reporting reduced print-specific tuning of the N1 in adults with a severe form of dyslexia (Helenius, Tarkiainen et al. 1999) and in young, reading-impaired children in a similar reading test (Maurer, Brem et al. 2007). Thus, our results provide support for an impairment in the fast, coarse form of visual tuning for print in dyslexic children, which in control children may be considered a first level of specialization of the VWF-system.

Absence of Orthographic Familiarity Effect in Dyslexic Children

Next, we investigated the specialization for visual print processing more closely by examining occipitotemporal activation in response to the three letter string types, leaving out the FF stimuli. We were able to demonstrate that the effect of orthographic familiarity on the activity of the VWF-system (i.e., higher activity for unfamiliar than for familiar word-forms) is not

detectable at any of the examined locations in the VWF-system of dyslexic children.

The present study significantly extends previous studies (Mechelli, Gorno-Tempini et al. 2003; Kronbichler, Bergmann et al. 2007; Bruno, Zumberge et al. 2008) that found an effect of orthographic familiarity in adults and adolescents in two ways. First, it demonstrates that such an effect is already present in children who have only a few years of reading experience. Second, we demonstrated that this effect involves profiles extending over multiple areas located along the posterior-anterior axis of the occipitotemporal VWF-system, rather than being limited to the VWFA. This pattern of activation in the occipitotemporal cortex is indicative of a specialization of this region for processing familiar letter strings. Consistent with the concept of an 'orthographic input lexicon'-function of the VWFA (Kronbichler, Bergmann et al. 2007; Bruno, Zumberge et al. 2008), we propose that the stronger activity in the occipitotemporal cortex for PH and PW compared to W is caused by prolonged screening of the orthographic lexicon for a matching word entry. Our results therefore support the notion that the VWFA processes letter strings also at the whole-word level. This finding contrasts with previous studies demonstrating similar activation for W and PW in the VWFA (Dehaene, Le Clec et al. 2002; Wydell, Vuorinen et al. 2003) and adjacent areas (Vinckier, Dehaene et al. 2007), suggesting prelexical processing in the VWFA.

Unlike those studies of adults or adolescents which show that activity for PH and PW is equally increased in comparison to W, we found a significant difference between PH and PW. Our study is more careful in controlling response bias than previous studies with only three conditions (Kronbichler, Bergmann et al. 2007; Bruno, Zumberge et al. 2008; Wimmer, Kronbichler et al. personal communication). Given that response requirements may affect activation patterns, differences in task design between the current and previous studies might also explain differences in findings between these studies for the comparison of PH (requiring a 'yes' response) and PW (requiring a 'no' response) – i.e. we found lower activity for PW than PH, whereas previous studies found no difference between PH and

PW in left occipitotemporal regions (Kronbichler, Bergmann et al. 2007; Bruno, Zumberge et al. 2008).

Importantly, our data reveal that the orthographic familiarity effect is already present in control children after 4-5 years of reading experience, and extends over multiple regions in the occipitotemporal cortex rather than being confined to a specific region within the VWF-system (VWFA) (Kronbichler, Bergmann et al. 2007; Bruno, Zumberge et al. 2008). Some authors hypothesized that expertise increases with growing reading experience, which may result in an increasing difference between brain responses to familiar and unfamiliar word-forms (Bruno, Zumberge et al. 2008). The effect of orthographic familiarity is not specific for German speakers but can be generalized to other languages as it was found to occur not only in German (Kronbichler, Bergmann et al. 2007) but also in English (Bruno, Zumberge et al. 2008) orthography. However, for the future, it would be important to examine specifically the role of orthographic familiarity in dyslexia also in deeper orthographies such as English where the effects may well be more prominent.

Finally, the finding that this occipitotemporal brain system is less sensitive to orthographic familiarity in children with dyslexia corresponds closely to the results of a recent fMRI study with dyslexic adults and adolescents (Wimmer, Kronbichler et al. personal communication). However, in contrast to both Wimmer et al. and Shaywitz et al. (2002), we did not find a general underactivation of the occipitotemporal cortex (i.e. lower activation for all conditions in dyslexics than controls), possibly due to the fact that we examined young dyslexic children rather than adults and adolescents.

What is the Exact Nature of the VWF-System Dysfunction?

Unlike most previous fMRI studies that examined local activation differences, our approach was to examine differences in preferential processing (i.e. specialization for one stimulus type vs. another), and spatial response gradients or sensitivity profiles across multiple regions along the anterior-posterior axis of the occipitotemporal cortex in control children. This approach allowed us to reveal spatially distributed, differences concerning a meaningful functional architecture. Our finding of two types of processing in

the left occipitotemporal cortex in controls is in line with the results of a priming study by Dehaene et al. (2004). First, their finding of a posterior-to-anterior gradient of increasing invariance for letter location (i.e. from location-specific representation of letters in posterior regions to location-invariant representation of words in anterior regions) is comparable to our posterior-to-anterior gradient of increasing print specificity. Second, their finding of a case-invariant representation of letters in this region is comparable to our finding of the presence of the orthographic familiarity effect throughout the occipitotemporal VWF-system.

Subsequently, we investigated whether dyslexia affected this preferential processing. Our results suggest that the dysfunction of the occipitotemporal cortex is characterized by a disturbance in both *functional* and *spatial* organization along its posterior-to-anterior axis. We are able to demonstrate that multiple regions along the posterior-to-anterior axis of the VWF-system are affected, rather than just its well-known core area i.e. the VWFA proper. To the best of our knowledge, this is the first study to demonstrate impaired specialization of the VWF-system in dyslexic children at both coarse, low-level (print vs. visual control stimuli) and fine-grained high-level (orthographically familiar vs. unfamiliar, i.e. W vs. PH) word processing. Such deficits at multiple levels are in line with converging evidence that the occipitotemporal cortex has more than one function and responds to multiple levels of sublexical orthographical structures (Dehaene, Le Clec et al. 2002; Wydell, Vuorinen et al. 2003; Binder, Medler et al. 2006; Vinckier, Dehaene et al. 2007). Additionally, corresponding to previous findings, this same region shows sensitivity on the whole-word level as demonstrated by the effect of orthographic familiarity (Kronbichler, Bergmann et al. 2007; Bruno, Zumberge et al. 2008; Wimmer, Kronbichler et al. personal communication) and cross-modal priming effects (Buckner, Koutstaal et al. 2000; Klaver, Schnaidt et al. 2007).

While the whole brain analysis indicated a significant group difference for PH near the VWFA, the ROI analyses revealed only one significant group difference for an individual condition: for W in ROI5. This finding leads us to suggest that the impairment of the VWF-system mainly appears to involve deficient tuning, i.e. for a certain stimulus type relative to other stimulus

types (e.g., letter strings vs. false-font items, as well as familiar vs. unfamiliar word-forms) as encoded along the VWF-system, rather than a less specific, general underactivation of an occipitotemporal "skill zone" for word reading (Shaywitz, Shaywitz et al. 2002; Sandak, Mencl et al. 2004; Shaywitz, Skudlarski et al. 2007). We therefore propose that the concept of an occipitotemporal "skill zone" should be extended to involve spatial reorganization of functional specialization (which might be especially important during the first years of reading acquisition). Possibly, due to neuroanatomical abnormalities, the occipitotemporal cortex of dyslexic individuals is impaired in developing reading expertise (Kronbichler, Bergmann et al. 2007; Maurer, Brem et al. 2007; Shaywitz, Skudlarski et al. 2007). Thus, during the first years of reading acquisition, the occipitotemporal cortex might be subjected to functional and structural changes resulting in the posterior-to-anterior gradient with increasing specificity for print. Accordingly, a recent voxel based morphometric study found the left inferior occipitotemporal cortex to be one of several regions exhibiting reduced gray matter density in dyslexic adults and adolescents (Kronbichler, Wimmer et al. 2008). Such a dysfunction might affect both local specialization for processing print stimuli and the development of a more abstract representation of whole word units (i.e., an orthographic input lexicon) and interfere with several stages in reading acquisition. Future research on systematic changes in levels of word- and print processing in dyslexic individuals will further contribute to a deeper understanding of this impairment.

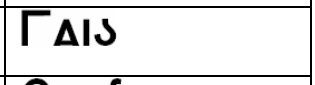
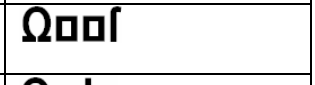
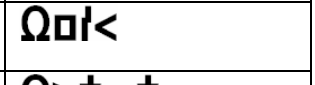
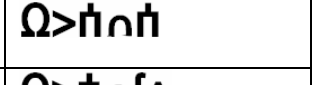
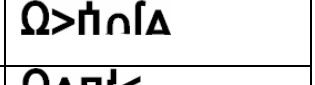
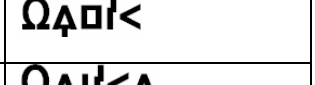
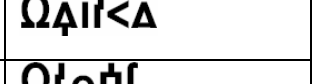
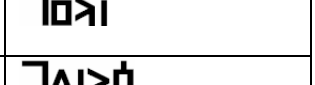
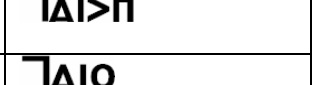
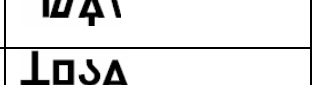
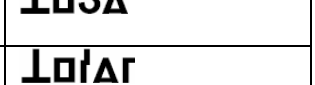
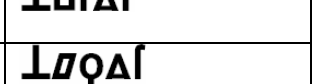
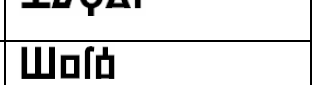
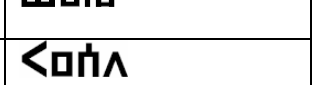
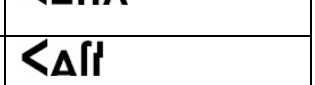
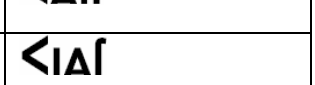
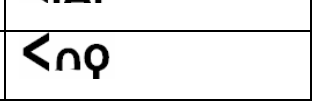
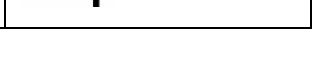
6.6 Acknowledgements

We wish to thank all children and their parents who participated in this study. This research was supported by the Neuroscience Center Zurich (ZNZ), the Swiss National Science Foundation (Project 32-108130) and the EU FP6 program NeuroDys.

6.7 Supplementary Material

*Supplementary Table 6.1. Com*plete List of Words, Pseudohomophones, Pseudowords and False-Fonts that were used in the Phonological Lexical Decision Task (in alphabetic order).

	Words	**Pseudohomophones**	**Pseudowords**	**False-Fonts**
1	Bad	Baad	Bud	ϴ□ὸ
2	Bart	Bard	Barl	ϴ□ɾɬ
3	Bein	Bain	Been	ϴΔIʌ
4	Blitz	Bliz	Blifz	ϴſlɬ<
5	Brei	Brai	Breg	ϴɾΔI
6	Brief	Brif	Brinf	ϴɾIΔ\
7	Durst	Dursd	Derst	Ǝ∩ɾɔɬ
8	Film	Vilm	Folm	◊lſж
9	Fuchs	Fux	Fochs	◊∩>ɦɔ
10	Geld	Gelt	Gelk	ΦΔſὸ
11	Gras	Graas	Gres	Φɾ□ɔ
12	Herz	Herts	Herk	ΠΔɾ<
13	Kaiser	Keiser	Kauser	Ш□ıɔΔɾ
14	Katze	Katse	Katpe	Ш□ɬ<Δ
15	Kerze	Kertse	Kerpe	ШΔɾ<Δ
16	Kleid	Klaid	Kleed	ШſΔıὸ
17	Klotz	Klots	Kletz	Шſ⍺ɬ<
18	Kohle	Kole	Kohne	Ш⍺ɦſΔ
19	König	Köhnig	Kunig	Ш⍺ʌıϙ
20	Kopf	Kobf	Kops	Ш⍺ϕ\
21	Leiter	Laiter	Lepter	ΛΔıɬΔɾ
22	Mehl	Mel	Mehg	ΨΔɦſ
23	Nase	Nahse	Nale	Λ□ɔΔ

24	Prinz	Brinz	Trinz	
25	Reis	Rais	Rels	
26	Saal	Sal	Saol	
27	Satz	Sats	Sanz	
28	Schuh	Schu	Schuw	
29	Schule	Schuhle	Schute	
30	Spatz	Spaz	Spotz	
31	Spitze	Spitse	Spotze	
32	Stuhl	Stul	Stuhn	
33	Taxi	Taksi	Tazi	
34	Teich	Taich	Tesch	
35	Teig	Taig	Teug	
36	Topf	Tobf	Tolf	
37	Vase	Wase	Vask	
38	Vater	Fater	Sater	
39	Vogel	Fogel	Wogel	
40	Wald	Walt	Walb	
41	Zahn	Zaan	Zarn	
42	Zelt	Zeld	Zelk	
43	Ziel	Tsiel	Zeel	
44	Zug	Zuhg	Zeg	

Supplementary Table 6.2. Main Activation Peaks Identified by Contrasting All Conditions with Fixation for Control Children and Children with Dyslexia.

Region	MNI Coordinates			*Z*	Voxels	BA
	x	*y*	*z*			
			Words > Fixation			
Control Children						
L Superior Frontal g.	0	6	60	6.60	1308	6
L Cingulate g.	-3	6	30	3.88		24
R Cingulate g.	6	-6	30	3.71		24
L Precentral g.	-42	-15	63	5.21	629	6
L Superior Temporal g.	-54	3	6	4.88	1397	22
L Insula	-36	-6	15	4.51		13
L Fusiform g.	-42	-51	-27	4.65	291	37
R Insula	45	3	3	4.21	226	13
R Superior Temporal g.	63	6	3	3.58		22
R Precentral g.	63	3	24	3.37	18	6
Children with Dyslexia						
Cerebellum	-39	-63	-33	5.20	640	-
L Fusiform g.	-42	-75	-27	4.93		19
L Inferior Occipital g.	-33	-87	-18	4.04		18
R Inferior Occipital g.	27	-93	-6	4.63	1445	18
L Medial Frontal g.	0	12	48	4.78	320	6
L Superior Frontal g.	-3	6	72	4.08		6
L Precentral g.	-36	-15	69	4.23	73	6
			Pseudohomophones > Fixation			
Control Children						
L Superior Frontal g.	0	6	60	6.60	1308	6
L Cingulate g.	-3	6	30	3.88		24
R Cingulate g.	6	-6	30	3.71		24
L Precentral g.	-42	-15	63	5.21	629	6
L Superior Temporal g.	-54	3	6	4.88	1397	22
L Insula	-36	-6	15	4.51		13
L Fusiform g.	-42	-51	-27	4.65	291	37

R Insula	45	3	3	4.21	226	13
R Superior Temporal g.	63	6	3	3.58		22
R Precentral g.	63	3	24	3.37	18	6
Children with Dyslexia						
L Medial Frontal g.	-3	15	51	5.72	5877	6
R Inferior Occipital g.	30	-93	-9	5.27	207	18
R Middle Occipital g.	42	-81	-3	2.86		19
L Fusiform g.	-42	-75	-21	4.13	546	19
L Superior Parietal l.	-27	-63	54	3.81	288	7
R Superior Parietal l.	30	-63	51	3.77	71	7
R Insula	33	21	6	3.71	71	13
L Inferior Frontal g.	-39	30	-18	3.36	23	47
R Middle Frontal g.	42	39	24	2.98	84	46
R Inferior Frontal g.	45	9	24	2.84	26	9
			Pseudowords > Fixation			
Control Children						
L Superior Frontal g.	0	15	54	6.76	6675	8
L Precentral g.	-51	0	51	5.88		6
L Inferior Frontal g.	-45	6	33	5.87		9
L Fusiform g.	-42	-51	-27	5.37	563	37
R Middle Frontal g.	48	33	18	4.03	471	46
R Superior Temporal g.	60	9	-3	3.51		22
R Inferior Frontal g.	48	6	33	4.55	224	9
R Superior Parietal l.	27	-60	39	3.12	28	7
Children with Dyslexia						
L Inferior Frontal g.	-60	6	21	6.00	6068	44
L Medial Frontal g.	0	12	51	5.96		6
R Cingulate g.	6	21	42	4.33		32
R Inferior Frontal g.	33	27	3	4.96	304	47
R Middle Occipital g.	33	-87	-3	3.74	163	18
R Inferior Occipital g.	27	-93	-9	3.58		18
L Precuneus	-27	-60	54	3.71	163	7
R Middle Frontal g.	42	45	30	3.48	23	10

L Superior Temporal g.	-66	-33	6	2.78	13	22
R Superior Temporal g.	63	-12	-3	2.60	12	21
False-Fonts > Fixation						
Control Children						
Cerebellum	30	-54	-33	5.46	301	-
R Middle Occipital g.	39	-84	-15	4.16		18
R Fusiform g.	39	-84	-15	4.16		19
L Precentral g.	-39	-18	69	5.19	103	6
L Postcentral g.	-54	-24	54	3.81		2
L Fusiform g.	-42	-72	-24	4.83	347	19
L Inferior Occipital g.	-36	-84	-27	4.19		18
L Medial Frontal g.	-3	0	57	4.13	45	6
L Insula	-45	-3	6	3.45	25	13
Children with Dyslexia						
No significant clusters						
Words > Fixation						
Controls vs. Dyslexics						
No significant clusters						
Pseudohomophones > Fixation						
Controls vs. Dyslexics						
L Insula	-42	-3	-3	4.56	268	13
L Inferior Parietal l.	-60	-30	39	4.35	102	40
R Insula	42	3	3	4.06	58	13
R Postcentral g.	66	-24	33	3.97	78	2
L Middle Frontal g.	-42	42	-6	3.92	35	47
R Middle Frontal g.	48	30	18	3.57	14	46
R Inferior Parietal l.	57	-42	39	3.53	20	40
L Fusiform g.	-45	-48	-24	3.41	18	37
Pseudowords > Fixation						

Controls vs. Dyslexics						
L Inferior Parietal l.	-60	-30	39	3.71	73	40
False-Fonts > Fixation						
Controls vs. Dyslexics						
No significant clusters						

MNI coordinates (*x/y/z*) are listed for local maxima of significant clusters ($p < 0.001$, uncorrected for multiple comparisons). *Z*-values are listed for voxels at the local maxima. BA is the Brodmann area nearest to the coordinate and should be considered approximate (L is left hemisphere, R is right hemisphere, g. is gyrus, l. is lobule).

Supplementary Table 6.3. Main Activation Peaks Identified by Contrasting Words with the Other Three Conditions for Control Children and Children with Dyslexia.

Region	MNI Coordinates			*Z*	Voxels	BA
	x	*y*	*z*			
	Words > False-Fonts					
Control Children						
L Inferior Frontal g.	-39	21	6	5.04	1366	45
L Insula	-48	9	3	4.63		13
L Medial Frontal g.	-3	24	48	3.56	90	8
L Superior Frontal g.	-3	12	60	3.35		6
R Inferior Frontal g.	33	27	3	3.43	16	47
Children with Dyslexia						
L Superior Frontal g.	-3	15	54	5.13	661	8
L Inferior Frontal g.	-51	27	18	4.42	1187	46
L Middle Frontal g.	-39	3	60	4.25		9
R Lingual g.	15	-54	0	4.40	2596	18
Cerebellum	18	-72	-33	4.33		-
R Inferior Frontal g.	39	24	-3	3.66	27	47
	False-Fonts > Words					
Control Children						
L Fusiform g.	-36	-81	-18	4.34	104	19
L Middle Occipital g.	-48	-78	-9	3.23		19
L Middle Occipital g.	-27	-96	6	3.16	12	18
R Superior Occipital g.	36	-84	30	3.49	44	19
Children with Dyslexia						
R Inferior Parietal l.	66	-36	36	3.15	14	40
	Pseudohomophones > Words					
Control Children						
L Superior Parietal l.	-33	-51	51	5.25	1185	7
L Precuneus	-24	-78	27	4.71		31
L Inferior Frontal g.	-45	6	33	4.92	2423	9

L Precentral g.	-51	-3	51	4.71		6
R Inferior Parietal l.	54	-36	57	4.42	545	40
R Superior Parietal l.	27	-72	45	3.86		7
L Medial Frontal g.	-3	0	60	4.36	491	6
R Superior Frontal g.	3	12	60	4.06		6
L Fusiform g.	-48	-60	-24	4.12	268	37
L Middle Occipital g.	-45	-69	-12	4.07		37
R Cingulate g.	6	-3	30	3.39	28	24
R Inferior Frontal g.	24	27	-3	3.35	16	47
R Insula	33	21	0	3.32		13
Children with Dyslexia						
L Inferior Frontal g.	-39	6	30	4.60	392	9
L Middle Frontal g.	-48	0	45	3.86		6
R Superior Parietal l.	27	-66	48	3.94	62	7
L Superior Parietal l.	-24	-75	57	3.81	157	7
L Superior Frontal g.	-6	9	66	3.79	130	6
R Medial Frontal g.	15	27	36	3.70		9
R Inferior Frontal g.	54	12	24	3.52	54	45
			Words > Pseudohomophones			
Control Children						
No significant clusters						
Children with Dyslexia						
L Middle Frontal g.	-30	30	51	3.74	26	8
R Precuneus	9	-69	36	3.54	55	7
R Superior Temporal g.	57	-63	18	3.42	13	39
R Superior Frontal g.	27	39	48	3.41	14	8
R Inferior Parietal g.	48	-66	39	3.18	11	39
R Angular g.	51	-72	33	3.15		39
			Pseudowords > Words			
Control Children						
L Inferior Frontal g.	-51	12	21	5.08	2660	44
L Precentral g.	-45	-3	57	5.02		6

L Medial Frontal g.	-3	15	51	4.77		6
L Fusiform g.	-42	-42	-21	3.51	341	37
L Precuneus	-21	-60	48	3.98	234	7
L Inferior Parietal l.	-33	-45	48	3.64		40
R Superior Frontal g.	36	51	21	3.65	75	10
R Middle Frontal g.	39	42	27	3.34		10
L Postcentral g.	-63	-21	30	3.36	33	2
L Superior Temporal g.	-60	-39	9	3.46	31	22
Children with Dyslexia						
L Inferior Frontal g.	-48	12	21	5.44	1362	44
L Precentral g.	-51	-6	45	5.30		6
L Superior Frontal g.	-6	9	57	4.83	378	6
R Cingulate g.	12	24	33	3.37		32
L Lingual g.	-33	-60	-3	3.46	116	19
L Middle Occipital g.	-36	-87	3	3.22		19
L Superior Parietal l.	-24	-60	57	3.66	28	7
		Words > Pseudowords				
Control Children						
L Superior Frontal g.	-36	21	54	4.86	118	8
L Inferior Parietal l.	-54	-66	39	4.38	158	39
L Angular g.	-54	-72	30	4.21		39
L Cingulate g.	-6	-36	39	4.32	214	31
R Cingulate g.	15	-45	39	4.09		31
L Insula	-45	-12	0	4.12	97	13
R Angular g.	51	-72	33	4.08	80	39
R Superior Temporal g.	60	-60	24	3.75		39
L Medial Frontal g.	-15	48	0	3.80	24	10
Children with Dyslexia						
L Superior Frontal g.	-15	24	60	4.63	171	6
R Inferior Parietal l.	48	-69	42	4.44	116	39
L Angular g.	-51	-72	33	4.16	270	39
L Precuneus	-36	-84	36	3.99		19
R Cingulate g.	9	-3	42	3.78	50	24

L Cingulate g.	-6	-30	42	3.40	15	31

MNI coordinates (*x/y/z*) are listed for local maxima of significant clusters ($p < 0.001$, uncorrected for multiple comparisons). *Z*-values are listed for voxels at the local maxima. BA is the Brodmann area nearest to the coordinate and should be considered approximate (L is left hemisphere, R is right hemisphere, g. is gyrus, l. is lobule).

Supplementary Table 6.4. Main Activation Peaks Identified by Contrasting Control Children and Children with Dyslexia for each Main Comparison of the Conditions.

Region	MNI Coordinates			*Z*	Voxels	BA
	x	*y*	*z*			
	False-Fonts > Words					
Controls vs. Dyslexics						
R Posterior Cingulate	15	-51	9	3.73	126	29
L Cuneus	-3	-75	12	3.50	45	18
L Posterior Cingulate	-15	-66	15	3.35		31
L Inferior Occipital g.	-33	-84	-21	3.27	21	18
L Middle Occipital g.	-42	-78	-15	3.22		18
	Pseudohomophones > Words					
Controls vs. Dyslexics						
L Inferior Parietal l.	-60	-33	39	3.77	56	40
L Insula	-45	-3	3	3.68	77	13
L Superior Temporal g.	-45	3	-9	3.41	45	38
	Pseudowords > Words					
Controls vs. Dyslexics						
No significant clusters						

MNI coordinates (*x/y/z*) are listed for local maxima of significant clusters ($p < 0.001$, uncorrected for multiple comparisons). *Z*-values are listed for voxels at the local maxima. BA is the Brodmann area nearest to the coordinate and should be considered approximate (L is left hemisphere, R is right hemisphere, g. is gyrus, l. is lobule).

7. Study B

The Ventral Visual Stream in Reading: Evidence from Functional Connectivity Patterns in Dyslexic Children and in Controls

Sanne van der Mark[1]*, Peter Klaver[1]*, Kerstin Bucher[1], Urs Maurer[2,3], Enrico Schulz[2,4], Silvia Brem[2,5], Thomas Loenneker[1,6], Ernst Martin[1,6], Daniel Brandeis[2,6]

* *The first and second authors contributed equally to this work.*

Author addresses:

[1] *MR-Center, University Children's Hospital, University of Zurich, Zurich, Switzerland*

[2] *Department of Child and Adolescent Psychiatry, University of Zurich, Zurich, Switzerland*

[3] *Sackler Institute for Developmental Psychobiology, Weill Medical College of Cornell University, New York, USA*

[4] *Department of Neurology, Technische Universität München, (81675) München, Germany*

[5] *Agora Center, University of Jyväskylä, Jyväskylä, Finland*

[6] *Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland*

Corresponding Author:

Daniel Brandeis, Department of Child and Adolescent Psychiatry, Brainmapping Research, Neumunsterallee 9, CH-8032 Zurich, Switzerland, phone: +41 43 499 2763, fax: +41 43 499 2604, E-mail: brandeis@kjpd.uzh.ch

Submitted to: Journal of Neuroscience.

Abstract

Developmental dyslexia is a severe reading disorder which is characterized by dysfluent reading due to impaired automaticity of visual word processing. Adults with dyslexia show functional deficits in the so called “Visual Word Form Area” (VWFA), a brain region implicated in visual word processing and located within the larger left occipitotemporal VWF-system. Previous studies investigating interregional cooperation during reading have focussed on the left angular gyrus and on reading problems in adults. The present study is the first to examine functional connections of the left occipitotemporal VWF-System with other major language areas in children with dyslexia. Functional MRI was used to assess connectivity for five neighbouring left occipitotemporal regions of interest (ROIs) during phonological and orthographic processing of visual word forms in 18 dyslexic and 24 age-matched control children (age 9.7-12.5 years). First, the results revealed that mainly the VWFA was functionally connected with typical left frontal and parietal language areas in control children. Adjacent posterior and anterior VWF-System ROIs did not show such connectivity, confirming the special role that the VWFA plays in word processing. Second, we detected a significant disruption of functional connectivity between the VWFA and left inferior frontal and left inferior parietal language areas in the dyslexic children. We propose that functional disconnection of a specific left occipitotemporal region crucial for automatic visual word processing (the VWFA) emerges early during reading acquisition in dyslexic children, possibly corresponding to their deficits in orthographic and phonological processing of visual word forms.

7.1 Introduction

Developmental dyslexia is a severe, specific disorder of reading acquisition with a high prevalence and familial risk (Schulte-Körne 2001). Converging evidence from neuroimaging studies investigating dyslexia suggests both structural and functional deficits in brain regions involved in reading, including left inferior frontal gyrus, left parietotemporal cortex and left occipitotemporal gyrus (for reviews see (Eckert 2004; Shaywitz and Shaywitz 2005)). Next to the well-documented phonological core deficit in dyslexia, another major deficit in individuals with dyslexia is the impaired automaticity of visual word processing, which prevents skilled, fluent (automatic) reading. Neuroimaging studies investigating dyslexia in adults suggest that this impairment is associated with a dysfunction of the left ventral occipitotemporal cortex (for a review see (Shaywitz and Shaywitz 2005)) including the so called Visual Word Form Area (VWFA; (Cohen, Dehaene et al. 2000; Dehaene, Jobert et al. 2004)). This brain region responds automatically and rapidly to visually presented words (Price, Moore et al. 1996) and is crucially involved in visual word recognition (Cohen, Jobert et al. 2004; Dehaene, Jobert et al. 2004). Recently, the VWFA has been shown to be part of a larger left occipitotemporal system critically involved in processing orthographic representations of visual letter-strings (Fernandez, Heitkemper et al. 2001; James, James et al. 2005; Mechelli, Crinion et al. 2005; Brem, Bucher et al. 2006; Vinckier, Dehaene et al. 2007; Van der Mark, Bucher et al. submitted). This so called VWF-system in the ventral visual stream is the main focus of the present study. Earlier neuroimaging studies have provided indications for the existence of a hierarchy for visual word processing in this ventral visual parthway, progressing from simple letter percept in occipital cortex to more complex features in anterior inferior temporal regions (Puce, Allison et al. 1996; Vandenberghe, Price et al. 1996; Indefrey, Kleinschmidt et al. 1997; Hagoort, Indefrey et al. 1999; Tarkiainen, Helenius et al. 1999; Cohen, Dehaene et al. 2000; Fernandez, Heitkemper et al. 2001). More recently, a posterior to anterior gradient of increasing print specificity was found in the left ventral occipitotemporal VWF-system in adults (Brem, Bucher et al. 2006; Vinckier, Dehaene et al. 2007) and adolescents (Brem, Bucher et al. 2006).

Furthermore, an fMRI study investigating effective connectivity during reading revealed that variations in prefrontal activity in response to regular words, exception words, and pseudo-words were associated with a selective increase in effective connectivity from distinct occipitotemporal areas (posterior, middle, anterior fusiform), depending on word-type (Mechelli, Crinion et al. 2005). Together, these results provide evidence for the important role that the left hemispheric ventral visual stream plays in reading. However, it has never been systematically investigated how distinct areas within this VWF-system are functionally connected with frontal and parietal regions within the language network of normal-reading children and whether this connectivity is disturbed in children with dyslexia.

Most previous studies using functional magnetic resonance imaging (fMRI) to investigate dyslexia applied conventional analyses to localize where task-related modulations of the blood oxygen level dependent (BOLD) signal differ between dyslexia and control groups. However, since impaired processing was found in several distrubuted brain regions (for a review see (Shaywitz and Shaywitz 2005)), dyslexia might be associated with a failure of multiple brain regions in working together properly during reading. Therefore, the analysis of network properties may contribute significantly to a better understanding of the neurobiological basis of this reading disorder.

A popular method for the examination of the cooperation between brain regions is called functional connectivity MRI (fcMRI). This data-driven analysis allows the identification of interregional correlations in low-frequency (<0.1 Hz) spontaneous BOLD fluctuations in the brain which cannot be attributed to manipulations in the experimental paradigm (Horwitz, Grady et al. 1992; Biswal, Yetkin et al. 1995; Friston 1995; Lowe, Mock et al. 1998; Xiong, Parsons et al. 1999; Arfanakis, Cordes et al. 2000; Cordes, Haughton et al. 2000; Fox and Raichle 2007). FcMRI is applied when the subject is in the same mental state, i.e. during a continuous resting state or continuous performance of a task (e.g. a reading task). Since this technique involves the calculation of correlation between signal changes in a seed region and signal changes in other parts of the brain, it can reveal functional interactions between brain areas but cannot establish a direct, causal relationship between brain regional activity (Friston, Frith et al.

1996). This is different from analyses of effective connectivity that test for unidirectional modulatory influences of a small number of brain regions upon another, which are defined in a model based on prior knowledge (e.g.,(Friston 1994; Bitan, Booth et al. 2005; Cao, Bitan et al. 2008)). Compared to effective connectivity, functional connectivity has the advantage that it is a data-driven rather than a hypothesis-driven type of analysis, thus not reducing its validity to the validity of the model (Friston 1994). Furthermore, compared to conventional fMRI analyses, functional connectivity analyses have the advantage that the results reflect co-variations with the effects of different stimulus categories statistically removed, and thus also depend less on systematic variations of the subject's performance related to the conditions (Xiong, Parsons et al. 1999; Arfanakis, Cordes et al. 2000). In addition, an event-related task was used in the present study, in which (in contrast to a blocked-design) the preparatory states are also expected to be stable over time, even though stimuli vary (Goebel, Roebroeck et al. 2003; Abler, Roebroeck et al. 2006). Evidence has been gathered from such functional networks between regions of the motor system (Biswal, Yetkin et al. 1995; Lowe, Mock et al. 1998; Xiong, Parsons et al. 1999; Cordes, Haughton et al. 2000; Jiang, He et al. 2004), the visual system (Biswal, Yetkin et al. 1995; Lowe, Mock et al. 1998; Cordes, Haughton et al. 2000), the auditory system (Cordes, Haughton et al. 2000), the memory network (Vincent, Snyder et al. 2006), and the language network (Horwitz, Rumsey et al. 1998; Pugh, Mencl et al. 2000; Hampson, Peterson et al. 2002).

Previous studies investigating interregional cooperation in adults with dyslexia have focussed mainly on the left angular gyrus. A functional disconnection of left angular gyrus with left inferior frontal gyrus and left fusiform gyrus was revealed in adults with dyslexia, regions that were functionally connected in controls during single word naming (Horwitz, Rumsey et al. 1998) and a non-word rhyming task (Pugh, Mencl et al. 2000). Furthermore, a recent fcMRI study extended these findings to other functional disconnections in cortical and cortical-cerebellar networks during a continuous phoneme-mapping task (Stanberry, Richards et al. 2006). Finally, in an fcMRI study investigating adults, Shaywitz et al. (2003) found

that normal readers exhibited functional connections between a left occipitotemporal region and inferior frontal gyrus, whereas poor readers demonstrated more functional connections between the left occipitotemporal region and right middle and inferior frontal gyri. Together, these findings suggest a disruption of the functional connectivity between left occipitotemporal, parietotemporal and left inferior frontal regions essential for fluent reading. However, since these studies only examined dyslexic adults rather than children who have not yet developed alternative reading strategies, they could not determine whether it constitutes a fundamental problem in dyslexia or is simply the result of compensation. Therefore, in order to understand the neurobiology of dyslexia, it is crucial to examine children in the early stages of reading acquisition.

The aim of the present study was to examine, for the first time, functional connectivity in children with dyslexia during a continuous phonological lexical processing task ("Does it sound like a real word?"), focussing on the systematic variations of connectivity in the VWF-system. Using a method called *seed-voxel correlation mapping* (Horwitz, Grady et al. 1992; Biswal, Yetkin et al. 1995), we studied the functional connectivity networks in children who were normal readers and dyslexics (mean age 11 years old) in order to understand both the normal patterns of connectivity for a reading-related language process and how these patterns of connectivity differ in children suffering from dyslexia. Based on converging evidence from fMRI studies of a critical impairment of the left occipitotemporal gyrus in dyslexia (for a review see (Shaywitz and Shaywitz 2005)), we selected five non-overlapping seed regions (Figure 7.1a): the VWFA of the fusiform gyrus (Cohen, Dehaene et al. 2000) and four adjacent areas along the posterior-anterior axes in the left hemisphere (Brem, Bucher et al. 2006; Van der Mark, Bucher et al. submitted). The four additional seed regions (two anterior and two posterior to the VWFA) were selected, in order to answer the question of specificity of possible functional connections between the VWFA and other language-related areas. We hypothesized that the left VWFA is functionally connected with left parietal and frontal language areas during visual word form processing in control children and that these functional connections are reduced in children with dyslexia. In addition, we

hypothesized that these functional connections would correlate with behavioural measures of reading ability within the control group. If such behavioural measures can be successfully related to brain connectivity, this would strengthen the hypothesis of a disconnection in dyslexic readers.

7.2 Materials and Methods

7.2.1 Participants

The 42 children who participated in this study were grouped according to their reading scores (see Table 7.1): 18 children with dyslexia and 24 control children (mean age 11.3 yrs, ±0.6yrs). Twenty-six children were part of an extensive longitudinal study investigating developmental dyslexia in children (Maurer, Bucher et al. 2003; Maurer, Brem et al. 2007; Schulz, Maurer et al. 2008; Van der Mark, Bucher et al. submitted) and 16 children participated only in either 4th or 5th grade. Six additional children were excluded from analysis: 1 child due to head movement exceeding the a-priori maximum movement criterion (> ±2 mm translation or > ±2° rotation), and 5 children because of poor task performance (accuracy < 60% in one or more conditions) – in order to make sure that the children had correctly understood the task instruction and were actually executing the task.

Subjects were submitted to a typical test battery for German dyslexia (Wimmer 1996; Mayringer and Wimmer 2000; Wimmer, Mayringer et al. 2000; Wimmer 2006) using the correct word-per-minute reading score as a reading fluency measure, which is the core criterion for diagnosing dyslexia in readers of the regular German orthography (Wimmer, Mayringer et al. 2000). The children tested in the 4th grade (n = 6), were grouped based on their "correct words per minute" reading score of the Salzburg Reading and Spelling Test ("Salzburger Lese- und Rechtschreibtest" (SLRT) (Landerl, Wimmer et al. 1997)), a test designed to assess dyslexia in children in 2nd to 4th grade. Reading skills of the children tested in 5th grade (n = 36) were assessed with the "Ein-Minuten Leseflüssigkeitstest" (Landerl and Willburger in press), which required the children to accurately read as many words as

possible from a list within 1 minute. The “correct words per minute” score of the 4th graders was compared to the published SLRT norms (Landerl et al., 1997), the “correct words per minute” score of the 5th graders was compared to the distribution in a normative group of 56 children, as detailed in (Schulz, Maurer et al. 2008). All children from the present fMRI study were categorized as dyslexic if their “correct words per minute”-score was below 10% of the norms (<61.6), and as controls if their score was equal or above 20% (<75.0). As can be seen in Table 7.1, the children with dyslexia performed worse not only on word reading (the criterion for grouping), but also on pseudoword reading.

Nonverbal and verbal intelligence was estimated using the block design and the similarities subtest of the HAWIK-III intelligence test (Tewes, Rossmann et al. 2000). The groups were matched for gender, age, and handedness. Furthermore, estimated verbal IQ did not differ between the groups and particularly non-verbal IQ was well-matched, as expected (Table 7.1). In addition, all parents filled out a questionnaire regarding the child’s handedness (Edinburgh Handedness Inventory (Oldfield 1971)). As a measure of phonological access to lexical store, all children performed a rapid automatic naming (RAN) task, including rapid naming of letters, digits and pictures with long and short object names (Landerl et al., personal communication). Finally, spelling scores consist of the mean % correctly written words of pooled SLRT scores of the 4th graders and DRT-5 scores (Diagnostischer Rechtschreibtest (Grund, Haug et al. 1995)) of the 5th graders.

The children were screened for a history of neurological diseases or psychiatric disorders and reported all normal or corrected-to-normal vision. Children from families with a foreign language background (i.e. both parents’ first language was not (Swiss-) German) were excluded from the study. The children were contacted by distributing handouts at schools. The children and their parents/caretakers gave their informed written consent to participate in the study. The study was approved by the local ethics committee.

Table 7.1. Demographic Characteristics of Controls and Children with Dyslexia and Group Differences (*t*-test or chi-square).

	Children with Dyslexia	Control Children	*P*-value
n	18	24	–
Age (years)	11.4 ± 0.7	11.3 ± 0.4	n.s.
Sex (male:female)	10:8	10:14	n.s.
Handedness (right:left)	15:3	17:7	n.s.
Estimated Verbal IQ	109 ± 11	114 ± 14	n.s.
Estimated Non-verbal IQ	111 ± 12	112 ± 11	n.s.
Correctly read W/min	49 ± 8	93 ± 16	$P < .001$
Correctly read PW/min	32 ± 5	54 ± 14	$P < .001$
Spelling	30 ± 23	86 ± 21	$P < .001$
RAN letter *z*	.60 ± .9	-.45 ± .8	$P = .001$
RAN picture (short) *z*	.43 ± 1.1	-.32 ± .8	$P = .021$
RAN picture (long) *z*	.53 ± .89	-.40 ± .9	$P = .002$
RAN digit *z*	.21 ± .9	-.16 ± 1.0	n.s.

Means and standard deviations (SD) are displayed; RAN: rapid automatic naming task, rate of pronouncing randomly presented letters, pictures with short or long object names, and digits in rows; *z*: *z*-scores mean = 0, SD = 1; Significant *p*-values indicate group differences (controls versus children with dyslexia); n.s.: non-significant.

7.2.2 Stimuli and Task

During fMRI acquisition, participants performed a phonological lexical decision task in which they had to decide if a visually presented stimulus sounded like a real word or not (Kronbichler, Bergmann et al. 2007; Van der Mark, Bucher et al. submitted). The 176 stimuli consisted of 44 orthographically familiar forms of German nouns (W), 44 pseudohomophones (PH; phonologically correct but orthographically unfamiliar forms of the same words), 44 pseudowords (PW; phonologically and orthographically unfamiliar forms) and 44 false-fonts (FF). Additionally, 65 null events (fixation cross only) were presented. The stimuli were presented in a pseudo-randomized fashion, and the order of the stimuli was the same for all participants.

The letter string stimuli (W, PH, PW) were adapted from those of Kronbichler et al. (Kronbichler, Bergmann et al. 2007) to accommodate the differences in German dialect (Swiss-German), and false-font (FF) strings were added as non-lexical control stimuli. For each letter, upper and lower case, a FF character was created. In contrast to previous studies (Kronbichler, Bergmann et al. 2007; Bruno, Zumberge et al. 2008), there were just as many trials requiring a "yes" response as a "no" response, due to the inclusion of the FF items. This excluded the possibility of a response bias toward "yes" responses. The characteristics of the four item types are shown in detail in Table 7.2. All stimuli were matched for complexity, character size, and number of characters in a string (3-6 characters; average horizontal visual angle: 2.2°, range: 1.3-3°). In addition, the letter string types were matched for bigram frequency.

In the event-related design, the stimuli were presented for 700 ms with an interstimulus interval (ISI) of 2550 ms during which a fixation cross was shown. Participants were instructed to press 'Yes' for W (e.g. Taxi) and PH (e.g. Taksi) and to press 'No' for PW (e.g. Tazi) and FF. For responding, they used the index finger and middle finger of their dominant hand. Yes- and No-Buttons were counterbalanced across participants and groups. Responses were made via a fiber-optics response button box (Lumina LP-400, Cedrus Corporation, San Pedro, USA) and stimulus delivery and response registration was controlled by Presentation (Neurobehavioral Systems Inc., Albany, CA, USA). To become familiar with the task, the subjects were given a short practice version (with different stimuli) of the task outside the scanner.

7.2.3 fMRI Acquisition

MRI data was acquired on a 3.0 T (GE Healthcare) whole-body scanner. For functional imaging, 535 functional images sensitive to BOLD contrast with 25 axial slices covering the whole brain were acquired with a T2*-sensitive multi-slice echo planar imaging (EPI) sequence (TR = 1.5s; TE = 31ms; FOV = 24cm; image matrix = 64 x 64; voxel size = 3.75 x 3.75 x 5 mm^3; flip angle = 50°). The first 4 scans were discarded to allow for equilibration effects. Participants were fitted with earplugs and viewed the stimuli via TFT video

goggles (Resonance Technology Inc., California, USA). Particular care was taken to stabilize the children by using vacuum cushions and custom made padding.

7.2.4 Behavioural data analysis

Response accuracy and reaction times (correct trials only) were analyzed separately in a repeated measures analysis of variance (ANOVA) with the within-subject factor 'condition' (W, PH, PW, FF) and between subject factor 'group' (controls and dyslexics children) (Table 7.2). Statistical analyses were performed using SPSS software (SPSS Inc., Chicago, USA).

7.2.5 Image preprocessing

Functional MRI data preprocessing and statistical analysis was done using SPM5 (Wellcome Department of Imaging Neuroscience, London, http://www.fil.ion.ucl.ac.uk/spm). The data were first motion corrected and the images were then normalized using a 4th Degree B-Spline interpolation method to match the Montreal Neurological Institute (MNI) EPI template. Finally, functional volumes were resampled to isotropic 3 mm^3 voxels and spatially smoothed with a 9 mm full width at half maximum isotropic Gaussian kernel.

7.2.6 Functional connectivity analyses

The initial step of the *seed-voxel correlation mapping* analysis was to define five non-overlapping seed regions of interest (ROIs) (Figure 7.1a), centered on the VWFA of the fusiform gyrus (Cohen, Dehaene et al. 2000) and covering neighbouring areas along a posterior-anterior axes in the left hemisphere. The coordinates were chosen in such a way that the ROIs would follow the slight anterior decline of the temporal lobe (Brem, Bucher et al. 2006; Van der Mark, Bucher et al. submitted): ROI1 (-42, -80, -14), ROI2 (-42, -68, -16), ROI3 (the VWFA; -42, -54, -17), ROI4 (-42, -42, -18), and ROI5 (MNI coordinates (*x/y/z*): -42, -30, -20).

In the next step, a mean time series for each ROI was computed for each subject individually using the MARSBAR toolbox (http://marsbar.sourceforge.net/) (Brett, Anton et al. 2002). In each subject

individually, the mean signal change in all 5 ROIs was then cross-correlated with the time series of all other voxels in the brain. Functional connectivity was calculated on residual time series by means of linear regression, after stimulus-related components were removed from the event-related data (Miezin, Maccotta et al. 2000; Schlaggar, Brown et al. 2002; Brown, Lugar et al. 2005; Fair, Brown et al. 2006). Based on the finding that measured event-related BOLD responses represent a linear superposition of spontaneous and stimulus-related activity in the human brain (Fox, Snyder et al. 2006), this enabled us to study interregional correlations in spontaneous BOLD fluctuations in the brain that were not dependent on the stimuli (Fox and Raichle 2007; Rogers, Morgan et al. 2007).

A total of nine orthogonal regressors (covariates of no interest) were used to reduce variance unlikely to reflect functional connectivity-related neuronal activity (Fox, Snyder et al. 2005; Villalobos, Mizuno et al. 2005; Fair, Schlaggar et al. 2007): six regressors corresponding to the six parameters obtained by the rigid body head motion correction; three regressors corresponding to the whole brain, white matter and ventricular (CSF) signal which included the averaged signals over voxels within the respective SPM template masks. Furthermore, four regressors related to the stimuli were included in order to minimize the stimulus-related variance (Miezin, Maccotta et al. 2000; Schlaggar, Brown et al. 2002; Brown, Lugar et al. 2005; Fair, Brown et al. 2006). To this end, the BOLD response time course for each stimulus condition (W, PH, PW and FF) was constructed by convolving the stimulus onsets of each stimulus type with the hemodynamic response function (HRF).

In the second-level analysis, a repeated measures ANOVA with within-subject factor 'ROI' (all five ROIs), and between subject factor 'group' (dyslexics and controls) was computed. The analysis allowed us to examine ROI-specific connectivity, since the inclusion of all five ROIs in the ANOVA controlled for connections that were non-specific for each ROI (connections common to all ROIs were statistically removed)[1]. For each of the five ROIs,

[1] Repeated measures ANOVA computed for each ROI separately did not show any additional connections to those already revealed by the ROI-specific analysis that included all five ROIs. See Supplementary Figure 7.1.

one-sample *t*-tests were computed on fit coefficients from the correlation analyses to yield functional connectivity maps for each group separately (controls and dyslexic children). Next, two-sample *t*-tests were computed to determine whether there were reliable group differences (control vs. dyslexic children) in functional connectivity. The group comparisons, representing the main focus of the present article, concentrated on the main areas showing connection with the VWF-system. To this end, the functional connectivity maps of group comparisons were masked with a mask including all significant clusters in both groups and all ROIs. For all statistical maps, a $P < 0.001$ uncorrected for multiple comparisons and a cluster size $k > 30$ were used to determine significant clusters of functional connectivity.

7.3 Results

7.3.1 Behavioural Results

Reaction time, accuracy and *p*-values of group comparisons for the phonological lexical decision task are reported in Table 7.2. In the phonological lexical decision task performed inside the scanner, accuracy scores differed significantly between conditions ($F(3,38) = 74.60$, $P < .001$) and groups ($F(1,40) = 13.68$, $P = .001$). In addition, an interaction of condition with group was found ($F(3,38) = 9.83$, $P < .001$). Post-hoc *t*-tests revealed that children with dyslexia made significantly more mistakes than control children for PH (more erroneous “no” responses) and for PW (more erroneous “yes” responses), whereas the groups performed equally well for W and FF.

Analysis of the reaction times yielded significant main effects of condition ($F(3,38) = 170.22$, $P < .001$) and group ($F(1,40) = 17.05$, $P < .001$) in addition to an interaction of condition with group ($F(3,38) = 21.09$, $P < .001$). Post-hoc *t*-tests revealed that the children with dyslexia responded more slowly than the control children to all three letter string conditions. Note that there was no significant group difference for FF.

Table 7.2. Performance During Phonological Lexical Decision Task and Item Characteristics.

Measures	Words	Pseudo-homophones	Pseudowords	False-Fonts
Task Performance				
Phonological lexical decision task (fMRI)				
Accuracy (%)				
Control children	94 (±7)	87 (±9)	91 (±8)	99 (±1)
Dyslexic Children	92 (±8)	80 (±9)	78 (±7)	98 (±3)
p-value	n.s.	*P* = .017	*P* < .001	n.s.
Reaction time (ms)				
Control children	1033 (±299)	1196 (±340)	1338 (±361)	837 (±227)
Dyslexic Children	1401 (±297)	1608 (±252)	1904 (±288)	895 (±198)
p-value	*P* < .001	*P* < .001	*P* < .001	n.s.
Orthographical judgment task				
Accuracy (%)				
Control children	93 (±19)	90 (±19)	95 (±20)	-
Dyslexic Children	90 (±5)	77 (±11)	96 (±4)	-
p-value	n.s.	*P* = .013	n.s.	-
Item Characteristics				
Number of characters	4.5 (± 0.7)	4.5 (± 0.8)	4.5 (± 1.0)	4.5 (± 0.7)
Bigram Frequency	11771 (± 8385)	10282 (± 9043)	11328 (± 9094)	-
Word Frequency	68.3 (± 74.2)	-	-	-

Means and standard deviations (SD) are displayed for the control, the dyslexic children and all four item types. Significant *p*-values indicate group differences; n.s.: non-significant.

7.3.2 Functional Connectivity MRI

Maps showing functional correlations of each separate ROI for both control and dyslexic children are shown in Figure 7.1b, and a detailed listing of the clusters showing significant interregional correlations is provided in Table 7.3. The global activation maxima of the ROI-based connectivity maps are

skipped in the activation tables and will not be further discussed. As expected, these maxima simply show that each ROI was highly autocorrelated (with *Z*-values being infinite).

Control Children

Figure 7.1b illustrates that, in control children, the VWFA seed region (ROI3) is functionally connected with brain areas of the traditional left-hemispheric language network (left inferior frontal gyrus and inferior parietal lobule) as well as right hemispheric inferior frontal gyrus and superior parietal lobule. By contrast, the four ROIs located anteriorly and posteriorly to the VWFA, revealed functional connectivity with different brain regions. For ROI1, being the most posterior ROI in the VWF-system, significant connectivity clusters were observed mainly in the left middle occipital gyrus. For ROI2, a large cluster of connectivity was found in left superior parietal lobule, similar to ROI3. Next, ROI4 showed significant functional connections with left insula and right superior temporal and fusiform gyrus. For ROI5, being the most anterior ROI in the VWF-system, significant connectivity clusters were observed in left fusiform gyrus and middle temporal gyrus. In a post-hoc analysis, the direct comparison of the functional connections for ROI3 in the control group with those for all other ROIs revealed significant clusters in left inferior frontal gyrus and inferior parietal lobule. These clusters were similar to those revealed by the group comparison for ROI3. This finding indicates that the functional connectivity with the language network was specific for the VWFA.

Children with Dyslexia

In the dyslexic group, ROI3 (VWFA) was found to correlate with middle occipital, middle temporal gyrus, and the thalamus in the left hemisphere. The most posterior ROI in the VWF-system (ROI1) correlated only with left inferior occipital gyrus. For ROI2, no significant correlation clusters were found. For ROI4, significant correlation clusters included left inferior occipital, superior temporal gyrus, and middle and inferior frontal gyrus. For the most anterior ROI in the VWF-system (ROI5), clusters were seen in left middle temporal gyrus, bilateral frontal gyrus, and right fusiform gyrus.

Group Comparison

The results of the group comparisons are shown in Figure 7.1c and Table 7.4. Functional connectivity in dyslexia was significantly reduced between the VWFA (ROI3) and left hemispheric language related regions, including inferior parietal lobule and inferior frontal gyrus. In contrast to the ROI located centrally within the left inferior occipitotemporal gyrus, greater connectivity for controls than dyslexics was not found for the two ROIs in early, low-level visual word processing areas of the VWF-system (ROI1 and ROI2) as well as for the two most anterior ROIs (ROI4 and ROI5).

Inverse effects, i.e., significantly greater connectivity for the dyslexic group in comparison to the control group, were observed between ROI3 and left middle temporal and middle occipital gyrus. Greater connectivity for dyslexics than controls for ROI4 was found mainly in left superior temporal gyrus and left insula. By contrast, such significant group differences could not be detected for the posterior ROIs 1 and 2 or in the most anterior ROI5.

Correlations between Connectivity and Behaviour

The finding of reduced connectivity of the VWFA with left inferior frontal gyrus and inferior parietal lobule in dyslexic children compared to controls raises the question whether it represents a disconnection syndrome or reflects a more general effect of reading ability. Thus, in a post-hoc analysis, we correlated − within the control group − the connectivity of two peak voxels (left inferior frontal gyrus and inferior parietal lobule) revealed by the contrast controls vs. dyslexics for ROI3 with several behavioural measures related to phonological processing. These behavioural measures included accuracy and reaction time scores for the four stimulus categories of the task performed during scanning, as well as behavioural measures acquired outside the scanner, i.e. pseudoword reading and picture naming. Results showed that the strength of the functional connections between the VWFA and left inferior frontal gyrus correlated significantly with reaction time for words (P = .041) during the phonological lexical decision task performed inside the scanner. The strength of these functional connections also correlated significantly with pseudoword reading (P = .040) and picture

naming (P = .019 for short object names; P = .022 for long object names) outside the scanner. The strength of the functional connections of the VWFA with left inferior parietal lobule correlated significantly with picture naming (P = .033 for short object names; P = .073 trend for long object names).

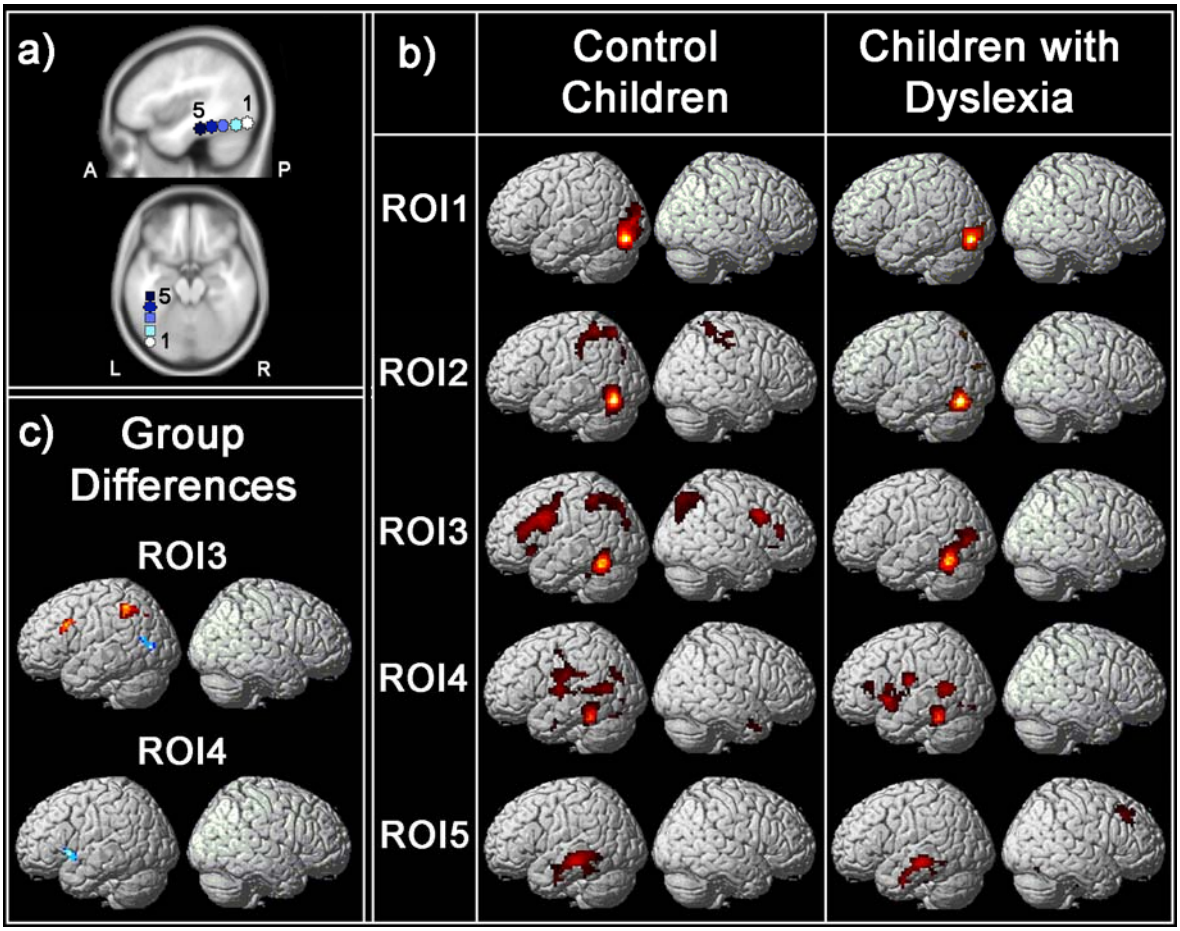


Figure 7.1. ROI-Specific Functional Connectivity Maps. a) Illustration of the 5 ROIs in the VWF-system: ROI1 (white) was located most posterior, ROI5 (black) most anterior in the left occipitotemporal cortex. ROI3 corresponds to the centre of the VWFA described in previous studies. **b)** Functional connectivity maps for control children, children with dyslexia, and **c)** the group comparison (red: controls > dyslexics, blue: dyslexics> controls) for all five ROIs separately. Significant clusters indicate the regions functionally connected with the corresponding left occipitotemporal ROI and were overlaid on a surface-rendered single subject brain normalized to MNI template. Statistical threshold was P < .001 uncorrected for multiple comparisons, k = 30. Maps of group comparison were masked with a group mask (see methods section for details).

7.4 Discussion

The present study examined functional connectivity in children with dyslexia during continuous orthographic processing, focussing on systematic variations of connectivity in the visual word-form area (VWFA; (Cohen, Dehaene et al. 2000)) and neighbouring regions within the left occipitotemporal VWF-system. This is the first study to use functional connectivity in children with dyslexia. Analysis of the behavioural data revealed that the children with dyslexia exhibited typically poor, dysfluent reading performance but were not impaired with false-font processing. These results indicate that children had problems with phonological decoding of visual letter strings varying in orthographic familiarity during the phonological lexical decision task.

The functional connectivity MRI data provide support for our main hypothesis that a functional disconnection exists early during reading acquisition in dyslexic children and is mainly linked to a specific left occipitotemporal region crucial for visual word processing (the VWFA). First, we found that the VWFA was functionally connected with typical left frontal and parietal language areas in the control children, whereas the adjacent posterior and anterior occipitotemporal ROIs in the VWF-system did not show significant connectivity with these distant regions of the language network. This finding suggests that these functional connections were specific for the VWFA and did not generalize to left occipitotemporal regions neighbouring the VWFA, confirming the special role that this region plays in print processing. Second, the group comparison revealed a significant disruption of functional connectivity in the VWF-system which was confined to these connections between the VWFA and left inferior frontal and inferior parietal reading-related brain regions in dyslexic children. Based on these results, we propose a focal disruption in functional connections between left hemispheric regions of the reading network involved in processing of visual word forms, which is already present during reading acquisition in children with dyslexia. This connectivity correlates with phonological performance inside and outside the scanner in the control group. This provides further

support that the reduced connectivity in the dyslexic group corresponds to their deficits in phonological processing.

ROI-specific functional connectivity in Control Children

The five left occipitotemporal VWF-system ROIs showed systematically different ROI-specific connections outside the VWF-system for controls and for children with dyslexia during orthographic processing of visual word-forms. The results for the control children revealed a separation of functional connectivity networks, depending on the posterior-anterior axis of the left inferior occipitotemporal gyrus. Specifically, the central left inferior occipitotemporal gyrus (ROI3), at the coordinates of the VWFA (Cohen, Dehaene et al. 2000), showed bilateral functional connections with other major components of the traditional language network (i.e. inferior parietal lobule and inferior frontal gyrus). By contrast, the two ROIs in early visual areas showed little connectivity with higher-order processing areas but were mainly connected with adjacent visual areas (ROI1), and left superior parietal lobule (ROI2), the latter suggesting involvement of visuospatial analysis and attention (for a review see (Kanwisher and Wojciulik 2000)). Furthermore, the two most anterior ROIs (ROI4 and ROI5) did not show interlobar connections but instead were connected with other temporal regions such as left insula (for ROI4) and left middle temporal gyrus (for ROI5), suggesting a link to auditory phonological or modality independent lexical-semantic processing (for reviews see: (Vigneau, Beaucousin et al. 2006; Lau, Phillips et al. 2008)). These results indicate that − within the ventral VWF-system − the VWFA may be the only that is connected to higher-order regions of the language network, which is in agreement with the belief that the left fusiform gyrus functions as a major relay of visual stimuli into the network, considering that it encodes a wide variety of complex visual percepts, including both verbal and nonverbal stimuli (Kanwisher, McDermott et al. 1997; Cohen, Dehaene et al. 2000; Haxby, Gobbini et al. 2001).

Disruption of ROI-specific Functional Connectivity in Children with Dyslexia

The group comparisons revealed that children with dyslexia showed significantly reduced ROI-specific functional connectivity between left inferior occipitotemporal gyrus (VWFA) and two major components of the language network: (i) left inferior parietal lobule and (ii) left inferior frontal gyrus. By revealing that a disconnection between these reading-related brain regions is already present in children with dyslexia, our findings significantly extend those of previous fcMRI studies in adults with dyslexia that showed that functional connectivity of left occipitotemporal gyrus with left angular gyrus was weaker (Horwitz, Rumsey et al. 1998; Pugh, Mencl et al. 2000) and connections between a left occipitotemporal seed region and left inferior frontal gyrus were absent during reading (Shaywitz, Shaywitz et al. 2003). In addition, our findings are consistent with a recent effective connectivity study demonstrating a weaker influence of left fusiform gyrus upon left inferior parietal lobule and left inferior frontal gyrus in dyslexic children compared to controls during a visual word rhyming task (Cao, Bitan et al. 2008). However, in contrast to the present study, Cao et al. investigated connectivity from a single location within the left fusiform gyrus rather than ROI-specific connectivity throughout the VWF-system, and due to the nature of the effective connectivity method, their analysis was more dependent on the model than that of the present study.

Post-hoc correlations of connectivity and behaviour revealed that the strength of the functional connectivity of the VWFA with especially left inferior frontal gyrus but also left inferior parietal lobule correlated inside the control group with performance measures of phonological processing. This indicates that the finding of a functional disconnection in children with dyslexia may reflect a more general phenomenon of reading ability. In other words, VWFA connectivity is weaker in poorer readers than in good readers, irrespective of whether they are explicitly categorized as dyslexic (Hampson, Tokoglu et al. 2006). This finding extends those of a previous fcMRI study demonstrating correlations between reading abilities of subjects and their functional connectivity between left angular gyrus and Broca's area (Hampson, Tokoglu et al. 2006). Furthermore, it is interesting that ROI-specific connectivity correlated significantly with reading and rapid naming

outside the scanner, particularly since this connectivity reflects spontaneous wide range covariation controlling for differences due to stimulus categories.

The finding of correlation between interregional functional connectivity and behavioural measures of phonological processing corresponds to the dyslexics' deficits in phonological processing of visual word-forms. Next to our findings of such a correlation, this interpretation is also based on findings from fMRI studies investigating normal reading found that left inferior parietal lobule is involved in integrating orthography and phonology (Geschwind 1965; Damasio and Damasio 1983; Friedman, Ween et al. 1993; Booth, Burman et al. 2002) and that left inferior frontal gyrus plays an important role in phonological processing (Pugh, Shaywitz et al. 1996; Fiez 1997; Poldrack, Wagner et al. 1999; Cabeza and Nyberg 2000; Price 2000; Friederici, Ruschemeyer et al. 2003). Furthermore, these regions were shown to exhibit abnormal activation during reading tasks in children with dyslexia (Temple, Poldrack et al. 2001; Shaywitz, Shaywitz et al. 2002; Cao, Bitan et al. 2006). Thus, we propose that children with dyslexia may not demonstrate functional connectivity of the VWFA with left inferior parietal lobule and left inferior frontal gyrus because they are not able to effectively engage these regions during the integration of orthography and phonology, and during phonological processing of written words, respectively.

The disruption in functional connectivity between the VWFA and left inferior parietal and inferior frontal cortex in dyslexic children indicates that brain regions necessary for fluent, skilled reading may not work together properly during reading. A probable explanation for this disruption in functional connectivity could be a disruption of anatomical connectivity. This hypothesis is supported by a study of a patient who developed pure alexia following a small surgical lesion close to his VWFA. The lesion, while leaving the VWFA anatomically uninjured, caused a disruption of the inferior longitudinal fasciculus (essential for normal reading, being the anatomical link between the VWFA and the occipital cortex), which resulted in pure alexia (Epelbaum, Pinel et al. 2008). However, it is still unknown how changes in anatomical connections of the VWFA are related to developmental dyslexia, since the study of Epelbaum et al. (2008) demonstrates anatomical disconnections in pure alexia, and most previous studies using diffusion

tensor imaging (Klingberg, Hedehus et al. 2000; Beaulieu, Plewes et al. 2005; Deutsch, Dougherty et al. 2005; Niogi and McCandliss 2006; Niogi and McCandliss 2006) and voxel-based morphometry (VBM) (Eckert, Leonard et al. 2005; Silani, Frith et al. 2005) have associated dyslexia with changes in anatomical connections of temporoparietal regions. To date, only one VBM study found reduced gray matter density in the left inferior occipitotemporal cortex in dyslexic adults and adolescents (Kronbichler, Wimmer et al. 2008). Accordingly, future studies combining techniques for examining functional and anatomical connections would be necessary to better understand the neurobiological basis of dyslexia.

Group differences in ROI-specific functional connectivity were largely confined to the VWFA. For this region, dyslexics demonstrated significantly greater connectivity than controls to left middle occipital and middle temporal gyrus. However, the ROI located directly anterior to the VWFA (ROI4) also demonstrated significantly increased connectivity for dyslexic children: to left superior temporal gyrus and left insula. These findings of great connectivity for dyslexics suggest increased auditory-phonological and lexical-semantic processing in children with dyslexia, possibly reflecting compensatory strategies. In contrast to these central ROIs, no group differences were found for the two most posterior ROIs (ROI1 and ROI2) or the most anterior ROI (ROI5) in the left occipitotemporal VWF-system. This suggests that children with dyslexia have normal functional connections in the lower-level visual areas of the VWF-system, in line with findings of fMRI studies in dyslexic adults (Booth et al., 2003a,b, 2004, 2007) and of event-related potential (ERP) studies in children with dyslexia at age 11 or 12 years (Brandeis, Vitacco et al. 1994; Simos, Breier et al. 2000).

7.4.1 Conclusion

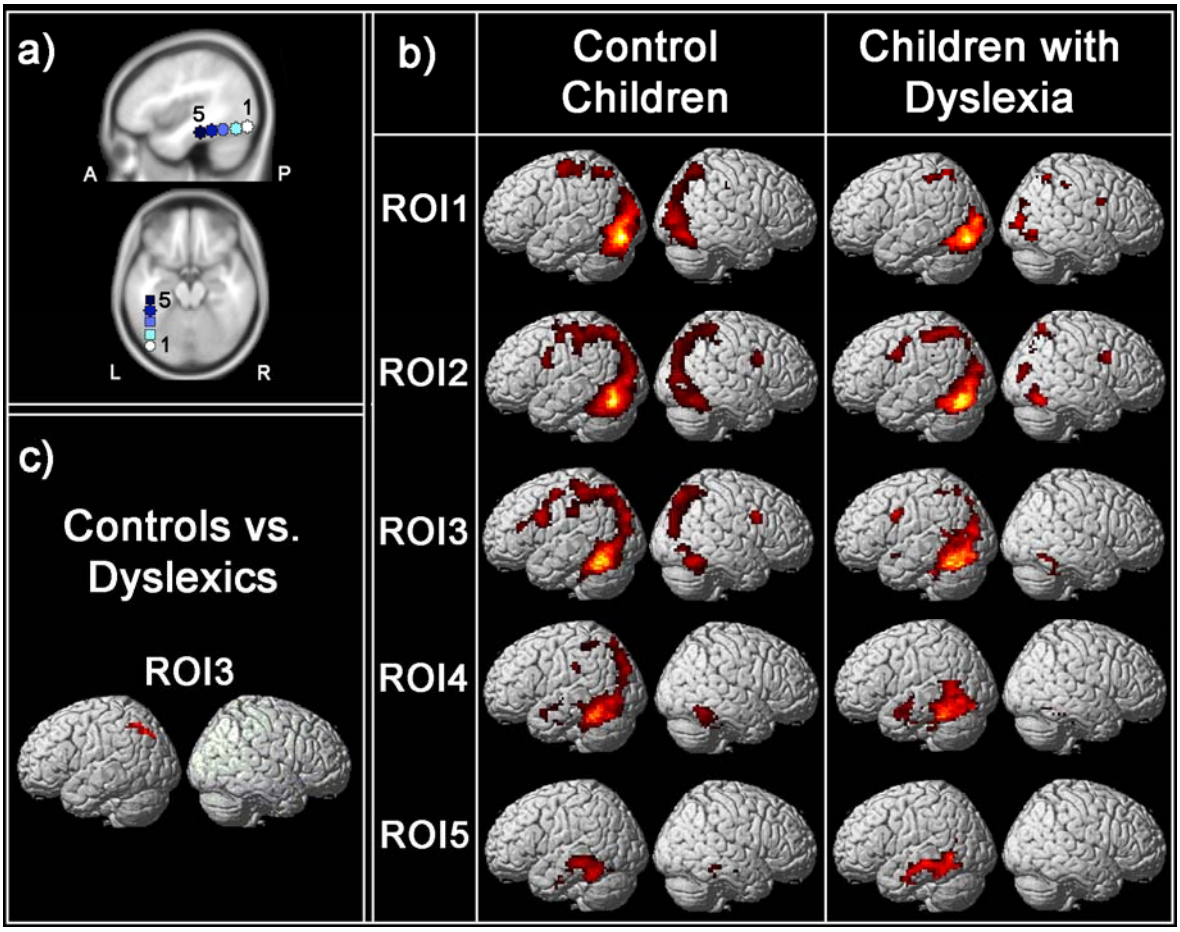
Functional connectivity between five neighbouring regions within the left occipitotemporal VWF-system involved in orthographic processing and other major components of the language network were compared in normal-reading children and children with dyslexia using seed-voxel correlation analysis. First, we revealed that specifically the VWFA was functionally

connected with typical left frontal and parietal language areas in control children, whereas the adjacent posterior and anterior occipitotemporal ROIs did not show such connectivity. Second, we detected a significant disruption of functional connectivity between the VWFA and left inferior frontal and left inferior parietal language areas in dyslexic children. We were able to show that this functional disruption may be linked to dyslexics' deficits in phonological processing. Furthermore, we found that greater connectivity for dyslexics than controls between the VWFA and a neighbouring region with other language areas, possibly reflecting compensatory strategies. Although the entire extent of the VWF-system was examined, our results seem to confirm the special role that the VWFA plays in visual word processing not only because of its functional connections with other major language areas in healthy children, but also because of the disruption of these connections in children with dyslexia.

7.5 Acknowledgement

This research was supported by the Neuroscience Center Zurich (ZNZ), the Swiss National Science Foundation (Project 32-108130), the EU FP6 program NeuroDys, and by the University of Zurich Research Priority Program "Integrative Human Physiology".

7.6 *Supplementary Material*



Supplementary Figure 7.1. Functional Connectivity Maps for Analyses of each ROI Separately. a) Illustration of the 5 ROIs in the VWF-system: ROI1 (white) was located most posterior, ROI5 (black) most anterior in the left occipitotemporal cortex. ROI3 corresponds to the centre of the VWFA described in previous studies. **b)** Functional connectivity maps for control children, children with dyslexia, and **c)** the group comparison for all five ROIs separately. Significant clusters indicate the regions functionally connected with the corresponding left occipitotemporal ROI and were overlaid on a surface-rendered single subject brain normalized to MNI template. Statistical threshold was $P < .001$ uncorrected for multiple comparisons, $k = 30$. Maps of group comparison were masked with a group mask (see methods section for details).

8. General Discussion

In this chapter, the key findings of the two studies will briefly be summarized, followed by a general discussion of the results with respect to the dysfunction and functional disconnection of the Visual Word Form-System in Children with dyslexia investigated in this thesis.

The main goal of the present work was to investigate the function and functional connectivity of the Visual Word Form (VWF) System in dyslexia, early during reading acquisition. For this purpose we investigated children with dyslexia and control children by means of fMRI and fcMRI techniques.

8.1 Disruption of Function of the VWF-system (Study A)

Dyslexia is a very heterogeneous disorder - impaired processing during reading has been found in several distributed brain regions (for a review see (Shaywitz and Shaywitz 2005)). The specific role that one of those impaired brain regions − the left occipitotemporal VWF-system − plays during reading is nevertheless still unclear. Consequently, further research is needed to better understand the exact nature of the dyslexia-related impairment of this region. In the first study (**Study A**) entitled "Children with Dyslexia lack Multiple Specializations along the Visual Word Form (VWF) System" we systematically investigated specialization within the VWF-system for processing both print and orthographic familiarity in children with and without dyslexia using fMRI. Our results revealed that control children show a dissociation of two functional levels of specialization within the VWF-system: (1) coarse specialization for print, i.e. differential processing of letter strings (real words, pseudohomophones and pseudowords) vs. visual control stimuli (false-fonts) and (2) sensitivity to orthographic familiarity, i.e. more efficient processing of familiar than unfamiliar visual word forms. Furthermore, we showed that both of these functional levels of VWF-system specialization could not be detected in children with dyslexia. Finally, we were able to demonstrate that the dysfunction in children with dyslexia

extends over the full range of the VWF-system along the posterior-anterior axis of the occipitotemporal gyrus.

The present study is the first to systematically examine multiple levels of specialization within the full extent of the VWF-system, by means of a phonological lexical decision task including three letter string types with varying orthographical familiarity and visual control stimuli, in children with dyslexia. This approach presents a considerable contribution to dyslexia research, since most previous studies focused either on the VWFA proper (Kronbichler, Bergmann et al. 2007; Bruno, Zumberge et al. 2008), examined adults with (Salmelin, Service et al. 1996; Rumsey, Horwitz et al. 1997; Rumsey, Nace et al. 1997; Brunswick, McCrory et al. 1999; Helenius, Tarkiainen et al. 1999; Paulesu, Demonet et al. 2001; Shaywitz, Shaywitz et al. 2003; McCrory, Mechelli et al. 2005; Wimmer, Kronbichler et al. personal communication) or without dyslexia (Brem, Bucher et al. 2006; Kronbichler, Bergmann et al. 2007; Vinckier, Dehaene et al. 2007; Bruno, Zumberge et al. 2008) rather than children with dyslexia. Furthermore, most previous studies have examined only one level of left occipitotemporal specialization for visual letter strings – fast, visual tuning for print (Helenius, Tarkiainen et al. 1999; Maurer, Brem et al. 2007) or sensitivity to orthographic familiarity (Mechelli, Gorno-Tempini et al. 2003; Kronbichler, Bergmann et al. 2007; Bruno, Zumberge et al. 2008; Wimmer, Kronbichler et al. personal communication) – and thus, by combining the two levels of specialization in one experimental design, the present study could significantly contribute to a better understanding of the exact function of this brain region during visual word processing.

8.2 Disruption of functional connectivity of the VWFA (study B)

Furthermore, as mentioned above, in consequence of the involvement of several regions in dyslexia, this reading disorder might be associated with a failure of multiple brain regions to work together properly during print processing. For this reason, the analysis of network properties of fMRI data may contribute significantly to a better understanding of the neurobiological basis of this reading disorder. In contrast to conventional fMRI analyses,

fcMRI computes interregional cooperation. Thus, based on the results of Study A and continuing our focus on the VWF-system, we investigated the cooperation between the separate areas of the VWF-system and other major reading-related regions, comparing children with dyslexia to normal-reading children in the fcMRI **Study B**, entitled "The Ventral Visual Stream in Reading: Evidence from Functional Connectivity Patterns in Dyslexic Children and in Controls". The aim of this study was to test the hypothesis that dyslexia is associated with a disruption of functional connections between the VWF-system and other regions of the language network. First, we found that, in control children, the functional connections with typical language areas (left inferior parietal lobule and left inferior frontal gyrus) were specific for the VWFA and did not generalize to left occipitotemporal regions neighbouring the VWFA. Second, we revealed that these functional connections are disrupted in children with dyslexia. Based on these results, we propose a focal disruption in functional connections between left hemispheric regions of the reading network involved in processing of visual word forms, which is already present during reading acquisition in children with dyslexia. Although the entire extent of the VWF-system was examined, our results seem to confirm the special role that the VWFA plays in print processing not only because of its functional connections with other major language areas in healthy children, but also because of the disruption of these connections in children with dyslexia. Based on findings of previous neuroimaging studies, we propose that the absence of these functional connections may correspond to the dyslexics' deficits in orthographic and phonological processing of visual word-forms.

The current study is the first to examine functional connections within the language network in children with dyslexia. Previous fcMRI studies have focussed on examining adults with (Horwitz, Rumsey et al. 1998; Pugh, Mencl et al. 2000; Shaywitz, Shaywitz et al. 2003; Stanberry, Richards et al. 2006) and without dyslexia (Hampson, Peterson et al. 2002; Hampson, Tokoglu et al. 2006). To date, there is only one study investigating connectivity between language areas in children with dyslexia (Cao, Bitan et al. 2008). Although our results are consistent with those of the study of Cao et al. (2008), the authors investigated connectivity from a single location

within the left fusiform gyrus rather than ROI-specific connectivity throughout the VWF-system. In addition, the effective connectivity method that Cao et al. used requires *a priori* definition of a model of unidirectional modulatory influences between a limited number of brain regions (e.g.,(Friston 1994; Bitan, Booth et al. 2005; Cao, Bitan et al. 2008)). Compared to the data-driven fcMRI analysis of the present study, their hypothesis-driven analysis therefore has the intrinsic disadvantage that it is dependent on the validity of the model.

8.3 Relation to neuroanatomical abnormalities

Together, the findings of Study A and B of a disruption in both function (of the VWF-system) and functional connectivity (between the VWFA and left inferior parietal and inferior frontal cortex) in dyslexic children indicate that brain regions necessary for fluent, skilled reading may not work together properly during reading. Possibly, due to neuroanatomical abnormalities, the occipitotemporal cortex of dyslexic individuals is impaired in developing reading expertise (Kronbichler, Bergmann et al. 2007; Maurer, Brem et al. 2007; Shaywitz, Skudlarski et al. 2007) and appropriate functional connections. Accordingly, a recent voxel based morphometric study found the left inferior occipitotemporal cortex to be one of several regions exhibiting reduced gray matter density in dyslexic adults and adolescents (Kronbichler, Wimmer et al. 2008), which may account for functional deficits in dyslexia. Such gray matter abnormalities might affect both local specialization for processing print stimuli and the development of a more abstract representation of whole word units (i.e., an orthographic input lexicon) and interfere with several stages in reading acquisition.

With respect to the disruption in functional connectivity, a probable explanation could be a disruption of anatomical connectivity. This hypothesis is supported by a study of a patient who developed pure alexia following a small surgical lesion close to his VWFA. The lesion, while leaving the VWFA anatomically uninjured, caused a disruption of the inferior longitudinal fasciculus (essential for normal reading, being the anatomical link between the VWFA and the occipital cortex), resulting in pure alexia

(Epelbaum, Pinel et al. 2008). However, it is still unknown how changes in anatomical connections of the VWFA are related to dyslexia, since the study of Epelbaum et al. (2008) demonstrates anatomical disconnections in pure alexia, and most previous studies using diffusion tensor imaging (Klingberg, Hedehus et al. 2000; Beaulieu, Plewes et al. 2005; Deutsch, Dougherty et al. 2005; Niogi and McCandliss 2006; Niogi and McCandliss 2006) and voxel-based morphometry (Eckert, Leonard et al. 2005; Silani, Frith et al. 2005) have associated dyslexia with changes in anatomical connections of temporoparietal regions but not of the VWFA.

8.4 Conclusion

In skilled reading orthographic processing (automatic recognition) of words is a crucial first step enabling subsequent higher-order processes such as phonological (grapheme-phoneme conversion) and semantical processing (analysis of the meaning of a word). When orthographic processing is impaired, the input into the language network is seriously corrupted and severe reading problems are the consequence. Further research on the role of the inferior occipitotemporal cortex in language processing in general and, more specifically, in orthographic processing is needed to adequately describe the nature of the functional deficit in dyslexia. In addition, future studies combining techniques for examining functional and anatomical connections would be necessary to better understand the neurobiological basis of dyslexia.

9. References

Abler, B., A. Roebroeck, et al. (2006). "Investigating directed influences between activated brain areas in a motor-response task using fMRI." Magn Reson Imaging **24**(2): 181-5.

Aghababian, V. and T. A. Nazir (2000). "Developing normal reading skills: aspects of the visual processes underlying word recognition." J Exp Child Psychol **76**(2): 123-50.

Arfanakis, K., D. Cordes, et al. (2000). "Combining independent component analysis and correlation analysis to probe interregional connectivity in fMRI task activation datasets." Magn Reson Imaging **18**(8): 921-30.

Beaulieu, C., C. Plewes, et al. (2005). "Imaging brain connectivity in children with diverse reading ability." Neuroimage **25**(4): 1266-71.

Binder, J. R., D. A. Medler, et al. (2006). "Tuning of the human left fusiform gyrus to sublexical orthographic structure." Neuroimage **33**(2): 739-48.

Biswal, B., F. Z. Yetkin, et al. (1995). "Functional connectivity in the motor cortex of resting human brain using echo-planar MRI." Magn Reson Med **34**(4): 537-41.

Bitan, T., J. R. Booth, et al. (2005). "Shifts of effective connectivity within a language network during rhyming and spelling." J Neurosci **25**(22): 5397-403.

Booth, J. R., G. Bebko, et al. (2007). "Children with reading disorder show modality independent brain abnormalities during semantic tasks." Neuropsychologia **45**(4): 775-83.

Booth, J. R., D. D. Burman, et al. (2002). "Functional anatomy of intra- and cross-modal lexical tasks." Neuroimage **16**(1): 7-22.

Brambati, S. M., C. Termine, et al. (2006). "Neuropsychological deficits and neural dysfunction in familial dyslexia." Brain Res **1113**(1): 174-85.

Brandeis, D., D. Vitacco, et al. (1994). "Mapping brain electric micro-states in dyslexic children during reading." Acta Paedopsychiatr **56**(3): 239-47.

Brem, S., K. Bucher, et al. (2006). "Evidence for developmental changes in the visual word processing network beyond adolescence." Neuroimage **29**(3): 822-37.

Brett, M., J. L. Anton, et al. (2002). Region of interest analysis using an SPM toolbox (Abstract). Presented at the 8th International Conference on Functional Mapping of the Human Brain; Sendai, Japan.

Brown, T. T., H. M. Lugar, et al. (2005). "Developmental changes in human cerebral functional organization for word generation." Cereb Cortex **15**(3): 275-90.

Bruck, M. (1992). "Persistence of Dyslexics' Phonological Awareness Deficits." Developmental Psychology **28**: 874–886.

Bruno, J. L., A. Zumberge, et al. (2007). "Sensitivity to Orthographic Familiarity in the Occipito-Temporal Region." NeuroImage **In Press**.

Bruno, J. L., A. Zumberge, et al. (2008). "Sensitivity to orthographic familiarity in the occipito-temporal region." Neuroimage **39**(4): 1988-2001.

Brunswick, N., E. McCrory, et al. (1999). "Explicit and implicit processing of words and pseudowords by adult developmental dyslexics: A search for Wernicke's Wortschatz?" Brain **122 (Pt 10)**: 1901-17.

Buchel, C. and K. Friston (2000). "Assessing interactions among neuronal systems using functional neuroimaging." Neural Netw **13**(8-9): 871-82.

Buckner, R. L., W. Koutstaal, et al. (2000). "Functional MRI evidence for a role of frontal and inferior temporal cortex in amodal components of priming." Brain **123 (Pt 3)**: 620-40.

Cabeza, R. and L. Nyberg (2000). "Imaging cognition II: An empirical review of 275 PET and fMRI studies." J Cogn Neurosci **12**(1): 1-47.

Cao, F., T. Bitan, et al. (2008). "Effective brain connectivity in children with reading difficulties during phonological processing." Brain Lang.

Cao, F., T. Bitan, et al. (2006). "Deficient orthographic and phonological representations in children with dyslexia revealed by brain activation patterns." J Child Psychol Psychiatry **47**(10): 1041-50.

Catts, H. W., M. E. Fey, et al. (2001). "Estimating the Risk of Future Reading Difficulties in Kindergarten Children: A Research-Based Model and Its Clinical Implementation." Language, Speech, and Hearing Services in Schools **32**: 38-50.

Cohen, L., S. Dehaene, et al. (2000). "The visual word form area: spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-brain patients." Brain **123 (Pt 2)**: 291-307.

Cohen, L., C. Henry, et al. (2004). "The pathophysiology of letter-by-letter reading." Neuropsychologia **42**(13): 1768-80.

Cohen, L., A. Jobert, et al. (2004). "Distinct unimodal and multimodal regions for word processing in the left temporal cortex." Neuroimage **23**(4): 1256-70.

Cohen, L., S. Lehericy, et al. (2002). "Language-specific tuning of visual cortex? Functional properties of the Visual Word Form Area." Brain **125**(Pt 5): 1054-69.

Cohen, L., O. Martinaud, et al. (2003). "Visual word recognition in the left and right hemispheres: anatomical and functional correlates of peripheral alexias." Cereb Cortex **13**(12): 1313-33.

Cordes, D., V. M. Haughton, et al. (2001). "Frequencies contributing to functional connectivity in the cerebral cortex in "resting-state" data." AJNR Am J Neuroradiol **22**(7): 1326-33.

Cordes, D., V. M. Haughton, et al. (2000). "Mapping functionally related regions of brain with functional connectivity MR imaging." AJNR Am J Neuroradiol **21**(9): 1636-44.

Damasio, A. R. and H. Damasio (1983). "The anatomic basis of pure alexia." Neurology **33**(12): 1573-83.

Dehaene, S., A. Jobert, et al. (2004). "Letter binding and invariant recognition of masked words: behavioral and neuroimaging evidence." Psychol Sci **15**(5): 307-13.

Dehaene, S., H. G. Le Clec, et al. (2002). "The visual word form area: a prelexical representation of visual words in the fusiform gyrus." Neuroreport **13**(3): 321-5.

Deutsch, G. K., R. F. Dougherty, et al. (2005). "Children's reading performance is correlated with white matter structure measured by diffusion tensor imaging." Cortex **41**(3): 354-63.

Dilling, H., W. Mombour, et al. (1993). International Classification of Mental Diseases, ICD-10. Bern, Huber.

Eckert, M. (2004). "Neuroanatomical markers for dyslexia: a review of dyslexia structural imaging studies." Neuroscientist **10**(4): 362-71.

Eckert, M. A., C. M. Leonard, et al. (2005). "Anatomical signatures of dyslexia in children: unique information from manual and voxel based morphometry brain measures." Cortex **41**(3): 304-15.

Epelbaum, S., P. Pinel, et al. (2008). "Pure alexia as a disconnection syndrome: new diffusion imaging evidence for an old concept." Cortex **44**(8): 962-74.

Fair, D. A., T. T. Brown, et al. (2006). "A comparison of analysis of variance and correlation methods for investigating cognitive development with functional magnetic resonance imaging." Dev Neuropsychol **30**(1): 531-46.

Fair, D. A., B. L. Schlaggar, et al. (2007). "A method for using blocked and event-related fMRI data to study "resting state" functional connectivity." Neuroimage **35**(1): 396-405.

Fernandez, G., P. Heitkemper, et al. (2001). "Inferior temporal stream for word processing with integrated mnemonic function." Hum Brain Mapp **14**(4): 251-60.

Fiez, J. A. (1997). "Phonology, semantics, and the role of the left inferior prefrontal cortex." Hum Brain Mapp **5**(2): 79-83.

Fox, M. D. and M. E. Raichle (2007). "Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging." Nat Rev Neurosci **8**(9): 700-11.

Fox, M. D., A. Z. Snyder, et al. (2005). "The human brain is intrinsically organized into dynamic, anticorrelated functional networks." Proc Natl Acad Sci U S A **102**(27): 9673-8.

Fox, M. D., A. Z. Snyder, et al. (2006). "Coherent spontaneous activity accounts for trial-to-trial variability in human evoked brain responses." Nat Neurosci **9**(1): 23-5.

Fox, P. T. and M. E. Raichle (1986). "Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects." Proc Natl Acad Sci U S A **83**(4): 1140-4.

Friederici, A. D., S. A. Ruschemeyer, et al. (2003). "The role of left inferior frontal and superior temporal cortex in sentence comprehension: localizing syntactic and semantic processes." Cereb Cortex **13**(2): 170-7.

Friedman, R. F., J. E. Ween, et al. (1993). Alexia. Clinical Neuropsychology, 3rd ed. K. M. Heilman and E. Valenstein. New York, Oxford University Press**:** 37–62.

Friston, K. J. (1994). "Functional and Effective Connectivity in Neuroimaging: A Synthesis." Human Brain Mapping **2**: 56-78.

Friston, K. J. (1995). "Functional and effective connectivity in neuroimaging: a synthesis." Hum Brain Mapp(2): 56-78.

Friston, K. J., C. D. Frith, et al. (1996). "Functional topography: multidimensional scaling and functional connectivity in the brain." Cereb Cortex **6**(2): 156-64.

Friston, K. J., C. D. Frith, et al. (1993). "Functional connectivity: the principal-component analysis of large (PET) data sets." J Cereb Blood Flow Metab **13**(1): 5-14.

Gauthier, I., M. J. Tarr, et al. (2000). "The fusiform "face area" is part of a network that processes faces at the individual level." J Cogn Neurosci **12**(3): 495-504.

Genovese, C. R., N. A. Lazar, et al. (2002). "Thresholding of statistical maps in functional neuroimaging using the false discovery rate." Neuroimage **15**(4): 870-8.

Geschwind, N. (1965). "Disconnexion syndromes in animals and man. I." Brain **88**(2): 237-94.

Goebel, R., A. Roebroeck, et al. (2003). "Investigating directed cortical interactions in time-resolved fMRI data using vector autoregressive modeling and Granger causality mapping." Magn Reson Imaging **21**(10): 1251-61.

Grund, M., G. Haug, et al. (1995). "DRT5 Diagnostischer Rechtschreibtest für 5. Klassen." Weinheim and Basel: Beltz.

Hagoort, P., P. Indefrey, et al. (1999). "The neural circuitry involved in the reading of German words and pseudowords: A PET study." J Cogn Neurosci **11**(4): 383-98.

Hampson, M., B. S. Peterson, et al. (2002). "Detection of functional connectivity using temporal correlations in MR images." Hum Brain Mapp **15**(4): 247-62.

Hampson, M., F. Tokoglu, et al. (2006). "Connectivity-behavior analysis reveals that functional connectivity between left BA39 and Broca's area varies with reading ability." Neuroimage **31**(2): 513-9.

Hasson, U., I. Levy, et al. (2002). "Eccentricity bias as an organizing principle for human high-order object areas." Neuron **34**(3): 479-90.

Haxby, J. V., M. I. Gobbini, et al. (2001). "Distributed and overlapping representations of faces and objects in ventral temporal cortex." Science **293**(5539): 2425-30.

Helenius, P., A. Tarkiainen, et al. (1999). "Dissociation of normal feature analysis and deficient processing of letter-strings in dyslexic adults." Cereb Cortex **9**(5): 476-83.

Henry, C., R. Gaillard, et al. (2005). "Brain activations during letter-by-letter reading: a follow-up study." Neuropsychologia **43**(14): 1983-9.

Hoeft, F., A. Meyler, et al. (2007). "Functional and morphometric brain dissociation between dyslexia and reading ability." Proc Natl Acad Sci U S A **104**(10): 4234-9.

Horwitz, B. and A. R. Braun (2004). "Brain network interactions in auditory, visual and linguistic processing." Brain Lang **89**(2): 377-84.

Horwitz, B., C. Grady, et al. (1992). "Functional associations among human posterior extrastriate brain regions during object and spatial vision." Journal of Cognitive Neuroscience **4**(4): 311-322.

Horwitz, B., J. M. Rumsey, et al. (1998). "Functional connectivity of the angular gyrus in normal reading and dyslexia." Proc Natl Acad Sci U S A **95**(15): 8939-44.

Indefrey, P., A. Kleinschmidt, et al. (1997). "Equivalent responses to lexical and nonlexical visual stimuli in occipital cortex: a functional magnetic resonance imaging study." Neuroimage **5**(1): 78-81.

James, K. H., T. W. James, et al. (2005). "Letter processing in the visual system: different activation patterns for single letters and strings." Cogn Affect Behav Neurosci **5**(4): 452-66.

Jäncke, L. (2005). Methoden der Bildgebung in der Psychologie und den kognitiven Neurowissenschaften. Stuttgart, Kohlhammer.

Jiang, T., Y. He, et al. (2004). "Modulation of functional connectivity during the resting state and the motor task." Hum Brain Mapp **22**(1): 63-71.

Jobard, G., F. Crivello, et al. (2003). "Evaluation of the dual route theory of reading: a metanalysis of 35 neuroimaging studies." Neuroimage **20**(2): 693-712.

Kanwisher, N., J. McDermott, et al. (1997). "The fusiform face area: a module in human extrastriate cortex specialized for face perception." J Neurosci **17**(11): 4302-11.

Kanwisher, N. and E. Wojciulik (2000). "Visual attention: insights from brain imaging." Nat Rev Neurosci **1**(2): 91-100.

Klaver, P., M. Schnaidt, et al. (2007). "Functional dissociations in top-down control dependent neural repetition priming." Neuroimage **34**(4): 1733-43.

Klingberg, T., M. Hedehus, et al. (2000). "Microstructure of temporo-parietal white matter as a basis for reading ability: evidence from diffusion tensor magnetic resonance imaging." Neuron **25**(2): 493-500.

Kronbichler, M., J. Bergmann, et al. (2007). "Taxi vs. Taksi: On Orthographic Word Recognition in the Left Ventral Occipitotemporal Cortex." J. Cogn. Neurosci. **19**(10): 1584-1594.

Kronbichler, M., F. Hutzler, et al. (2006). "Evidence for a dysfunction of left posterior reading areas in German dyslexic readers." Neuropsychologia **44**(10): 1822-32.

Kronbichler, M., H. Wimmer, et al. (2008). "Developmental dyslexia: Gray matter abnormalities in the occipitotemporal cortex." Hum Brain Mapp **29**(5): 613-25.

Landerl, K. and E. Willburger (in press). "Der Ein-Minuten Leseflüssigkeitstest – ein Verfahren zur Diagnose der Leistung im Wort- und Pseudowortlesen." Tests und Trends.

Landerl, K., H. Wimmer, et al. (1997). "The impact of orthographic consistency on dyslexia: a German-English comparison." Cognition **63**(3): 315-34.

Landerl, K., H. Wimmer, et al. (1997). "SLRT Salzburger Lese- und Rechtschreibtest (Salzburg Reading and Orthography Test)." Bern: Huber.

Lau, E. F., C. Phillips, et al. (2008). "A cortical network for semantics: (de)constructing the N400." Nat Rev Neurosci **9**(12): 920-33.

Logothetis, N. K., J. Pauls, et al. (2001). "Neurophysiological investigation of the basis of the fMRI signal." Nature **412**(6843): 150-7.

Logothetis, N. K. and B. A. Wandell (2004). "Interpreting the BOLD signal." Annu Rev Physiol **66**: 735-69.

Lowe, M. J., B. J. Mock, et al. (1998). "Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations." Neuroimage **7**(2): 119-32.

Lyon, G. R., S. E. Shaywitz, et al. (2003). "A Definition of Dyslexia." Ann Dyslexia **53**: 1-14.

Maisog, J. M., E. R. Einbinder, et al. (2008). "A meta-analysis of functional neuroimaging studies of dyslexia." Ann N Y Acad Sci **1145**: 237-59.

Maldjian, J. A., P. J. Laurienti, et al. (2003). "An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets." Neuroimage **19**(3): 1233-9.

Maurer, U., S. Brem, et al. (2005). "Emerging neurophysiological specialization for letter strings." J Cogn Neurosci **17**(10): 1532-52.

Maurer, U., S. Brem, et al. (2007). "Impaired tuning of a fast occipito-temporal response for print in dyslexic children learning to read." Brain **130**(Pt 12): 3200-10.

Maurer, U., S. Brem, et al. (2006). "Coarse neural tuning for print peaks when children learn to read." Neuroimage **33**(2): 749-58.

Maurer, U., K. Bucher, et al. (2003). "Development of the automatic mismatch response: from frontal positivity in kindergarten children to the mismatch negativity." Clin Neurophysiol **114**(5): 808-17.

Mayringer, H. and H. Wimmer (2000). "Pseudoname learning by German-speaking children with dyslexia: evidence for a phonological learning deficit." J Exp Child Psychol **75**(2): 116-33.

McCandliss, B. D., L. Cohen, et al. (2003). "The visual word form area: expertise for reading in the fusiform gyrus." Trends Cogn Sci **7**(7): 293-299.

McCrory, E. J., A. Mechelli, et al. (2005). "More than words: a common neural basis for reading and naming deficits in developmental dyslexia?" Brain **128**(Pt 2): 261-7.

Mechelli, A., J. T. Crinion, et al. (2005). "Dissociating reading processes on the basis of neuronal interactions." J Cogn Neurosci **17**(11): 1753-65.

Mechelli, A., M. L. Gorno-Tempini, et al. (2003). "Neuroimaging studies of word and pseudoword reading: consistencies, inconsistencies, and limitations." J Cogn Neurosci **15**(2): 260-71.

Miezin, F. M., L. Maccotta, et al. (2000). "Characterizing the hemodynamic response: effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing." Neuroimage **11**(6 Pt 1): 735-59.

Niogi, S. N. and B. D. McCandliss (2006). "Left lateralized white matter microstructure accounts for individual differences in reading ability and disability." Neuropsychologia **44**(11): 2178-88.

Niogi, S. N. and B. D. McCandliss (2006). "Left lateralized white matter microstructure accounts for individual differences in reading ability and disability." Neuropsychologia.

Ogawa, S., T. M. Lee, et al. (1990). "Brain magnetic resonance imaging with contrast dependent on blood oxygenation." Proc Natl Acad Sci U S A **87**(24): 9868-72.

Oldfield, R. C. (1971). "The assessment and analysis of handedness: the Edinburgh inventory." Neuropsychologia **9**(1): 97-113.

Paulesu, E., J. F. Demonet, et al. (2001). "Dyslexia: cultural diversity and biological unity." Science **291**(5511): 2165-7.

Paulesu, E., E. McCrory, et al. (2000). "A cultural effect on brain function." Nat Neurosci **3**(1): 91-6.

Pennington, B. and J. Gilger (1996). How is dyslexia transmitted? Developmental dyslexia. Neural, cognitive, and genetic mechanisms. C. Chase, G. Rosen and G. Sherman. Baltimore, MD, York Press**:** 41–61.

Poldrack, R. (2001). A structural basis for developmental dyslexia: evidence from diffusion tensor imaging. Dyslexia, fluency, and the brain. M. Wolf. Timonium (MD), York Press**:** 213–33.

Poldrack, R. A., A. D. Wagner, et al. (1999). "Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex." Neuroimage **10**(1): 15-35.

Price, C. J. (2000). "The anatomy of language: contributions from functional neuroimaging." J Anat **197 (Pt 3)**: 335-59.

Price, C. J., C. J. Moore, et al. (1996). "The effect of varying stimulus rate and duration on brain activity during reading." Neuroimage **3**(1): 40-52.

Price, C. J., R. J. Wise, et al. (1996). "Demonstrating the implicit processing of visually presented words and pseudowords." Cereb Cortex **6**(1): 62-70.

Puce, A., T. Allison, et al. (1996). "Differential sensitivity of human visual cortex to faces, letterstrings, and textures: a functional magnetic resonance imaging study." J Neurosci **16**(16): 5205-15.

Pugh, K. R., W. E. Mencl, et al. (2000). "Functional neuroimaging studies of reading and reading disability (developmental dyslexia)." Ment Retard Dev Disabil Res Rev **6**(3): 207-13.

Pugh, K. R., W. E. Mencl, et al. (2000). "The angular gyrus in developmental dyslexia: task-specific differences in functional connectivity within posterior cortex." Psychol Sci **11**(1): 51-6.

Pugh, K. R., B. A. Shaywitz, et al. (1996). "Cerebral organization of component processes in reading." Brain **119 (Pt 4)**: 1221-38.

Ramus, F., S. Rosen, et al. (2003). "Theories of developmental dyslexia: insights from a multiple case study of dyslexic adults." Brain **126**(Pt 4): 841-65.

Rogers, B. P., V. L. Morgan, et al. (2007). "Assessing functional connectivity in the human brain by fMRI." Magn Reson Imaging **25**(10): 1347-57.

Rumsey, J. M., B. Horwitz, et al. (1997). "Phonological and orthographic components of word recognition. A PET-rCBF study." Brain **120 (Pt 5)**: 739-59.

Rumsey, J. M., K. Nace, et al. (1997). "A positron emission tomographic study of impaired word recognition and phonological processing in dyslexic men." Arch Neurol **54**(5): 562-73.

Salmelin, R., E. Service, et al. (1996). "Impaired visual word processing in dyslexia revealed with magnetoencephalography." Ann Neurol **40**(2): 157-62.

Sandak, R., W. E. Mencl, et al. (2004). "The neurobiology of adaptive learning in reading: a contrast of different training conditions." Cogn Affect Behav Neurosci **4**(1): 67-88.

Schlaggar, B. L., T. T. Brown, et al. (2002). "Functional neuroanatomical differences between adults and school-age children in the processing of single words." Science **296**(5572): 1476-9.

Schulte-Körne, G. (2001). Lese-Rechtschreibstörung und Sprachwahrnehmung. Münster, Waxmann Verlag.

Schulz, E., U. Maurer, et al. (2008). "Impaired semantic processing during sentence reading in children with dyslexia: Combined fMRI and ERP evidence." Neuroimage **41**(1): 153-68.

Schumacher, J., P. Hoffmann, et al. (2007). "Genetics of dyslexia: the evolving landscape." J Med Genet **44**(5): 289-97.

Shaywitz, B. A., S. E. Shaywitz, et al. (2002). "Disruption of posterior brain systems for reading in children with developmental dyslexia." Biol Psychiatry **52**(2): 101-10.

Shaywitz, B. A., S. E. Shaywitz, et al. (2002). "Disruption of posterior brain systems for reading in children with developmental dyslexia." Biological Psychiatry **52**(2): 101-110.

Shaywitz, B. A., P. Skudlarski, et al. (2007). "Age-related changes in reading systems of dyslexic children." Ann Neurol **61**(4): 363-70.

Shaywitz, S. (2003). Overcoming Dyslexia: A New and Complete Science-Based Program for Reading Problems at Any Level. New York, Alfred A. Knopf.

Shaywitz, S. E., J. M. Fletcher, et al. (1999). "Persistence of dyslexia: the Connecticut Longitudinal Study at adolescence." Pediatrics **104**(6): 1351-9.

Shaywitz, S. E. and B. A. Shaywitz (2005). "Dyslexia (specific reading disability)." Biol Psychiatry **57**(11): 1301-9.

Shaywitz, S. E., B. A. Shaywitz, et al. (2003). "Neural systems for compensation and persistence: young adult outcome of childhood reading disability." Biol Psychiatry **54**(1): 25-33.

Silani, G., U. Frith, et al. (2005). "Brain abnormalities underlying altered activation in dyslexia: a voxel based morphometry study." Brain **128**(Pt 10): 2453-61.

Simos, P. G., J. I. Breier, et al. (2000). "Cerebral mechanisms involved in word reading in dyslexic children: a magnetic source imaging approach." Cereb Cortex **10**(8): 809-16.

Simos, P. G., J. I. Breier, et al. (2002). "Brain mechanisms for reading words and pseudowords: an integrated approach." Cerebral Cortex **12**(3): 297-305.

Stanberry, L. I., T. L. Richards, et al. (2006). "Low-frequency signal changes reflect differences in functional connectivity between good readers and dyslexics during continuous phoneme mapping." Magn Reson Imaging **24**(3): 217-29.

Tagamets, M. A., J. M. Novick, et al. (2000). "A parametric approach to orthographic processing in the brain: an fMRI study." J Cogn Neurosci **12**(2): 281-97.

Talairach, J. and P. Tournoux (1988). Co-planar stereotaxic atlas of the human brain. New York, Thieme.

Tarkiainen, A., P. Helenius, et al. (1999). "Dynamics of letter string perception in the human occipitotemporal cortex." Brain **122 (Pt 11)**: 2119-32.

Temple, E., R. A. Poldrack, et al. (2001). "Disrupted neural responses to phonological and orthographic processing in dyslexic children: an fMRI study." Neuroreport **12**(2): 299-307.

Tewes, U., P. Rossmann, et al. (2000). HAWIK-III Hamburg-Wechsler-Intelligenztest für Kinder [Wechsler intelligence scale for children (WISC-III; 1991)-German version]. Bern, Huber.

Turkeltaub, P. E., L. Gareau, et al. (2003). "Development of neural mechanisms for reading." Nat Neurosci **6**(7): 767-73.

Ungerleider, L. G. and J. V. Haxby (1994). "'What' and 'where' in the human brain." Curr Opin Neurobiol **4**(2): 157-65.

Van der Mark, S., K. Bucher, et al. (submitted). "Children with Dyslexia lack Multiple Specializations along the Visual Word Form (VWF) System."

Vandenberghe, R., C. Price, et al. (1996). "Functional anatomy of a common semantic system for words and pictures." Nature **383**(6597): 254-6.

Vigneau, M., V. Beaucousin, et al. (2006). "Meta-analyzing left hemisphere language areas: phonology, semantics, and sentence processing." Neuroimage **30**(4): 1414-32.

Villalobos, M. E., A. Mizuno, et al. (2005). "Reduced functional connectivity between V1 and inferior frontal cortex associated with visuomotor performance in autism." Neuroimage **25**(3): 916-25.

Vincent, J. L., A. Z. Snyder, et al. (2006). "Coherent spontaneous activity identifies a hippocampal-parietal memory network." J Neurophysiol **96**(6): 3517-31.

Vinckier, F., S. Dehaene, et al. (2007). "Hierarchical coding of letter strings in the ventral stream: dissecting the inner organization of the visual word-form system." Neuron **55**(1): 143-56.

Warrington, E. K. and T. Shallice (1980). "Word-form dyslexia." Brain **103**(1): 99-112.

Wimmer, H. (1996). "The nonword reading deficit in developmental dyslexia: evidence from children learning to read German." J Exp Child Psychol **61**(1): 80-90.

Wimmer, H. (2006). "Don't neglect reading fluency!" Dev Sci **9**(5): 447-8; discussion 451-3.

Wimmer, H., M. Kronbichler, et al. (personal communication). "Evidence for a Dysfunction of the Visual Word Form Area (VWFA) in Developmental Dyslexia."

Wimmer, H., M. Kronbichler, et al. (under revision). "Evidence for a Dysfunction of the Visual Word Form Area (VWFA) in Developmental Dyslexia."

Wimmer, H., H. Mayringer, et al. (2000). "The double-deficit hypothesis and difficulties in learning to read a regular orthography." Journal of Educational Psychology **92**(4): 668-680.

Wydell, T. N., T. Vuorinen, et al. (2003). "Neural correlates of letter-string length and lexicality during reading in a regular orthography." J Cogn Neurosci **15**(7): 1052-62.

Xiong, J., L. M. Parsons, et al. (1999). "Interregional connectivity to primary motor cortex revealed using MRI resting state images." Hum Brain Mapp **8**(2-3): 151-6.

Curriculum Vitae

Personal Data

Name	Sanne van der Mark
Address	Wiesenstrasse 2
Zip-Code	CH-8008 Zürich
Country	Switzerland
Date of Birth	08.05.1982
Place of Birth	Kerkrade, The Netherlands
Nationality	Dutch

Education and Qualifications

2005 – 2009 Ph.D. student at University Children's Hospital Zurich, Switzerland.
Ph.D. thesis title: "Deficits in Function and Functional Connectivity of Left Occipitotemporal Cortex in Children with Dyslexia".
Supervisors: Prof. Daniel Brandeis, Ph.D., Prof. Ernst Martin, M.D.

2005 - Center of Neuroscience Zurich, University / ETH Zurich, Switzerland.
Ph.D. Program in Neuroscience

2000 - 2005 MSc in Cognitive Neuroscience and Neuropsychology at Maastricht University, the Netherlands.
Master thesis title: "Suppression of Conscious Perception and Breakdown of Priming. The Effect of spTMS over Primary Visual Cortex during a Visual Masking Paradigm".
Supervisors: Alexander Sack, Ph.D., Prof. Rainer Goebel, Ph.D.

2003 Erasmus Student Exchange Program at the University of Salamanca, Spain.

2000 - 2003 Program comparable to BSc in Biological Psychology at Maastricht University.

1994 - 2000 High school in Kerkrade, the Netherlands.

Grants and Awards:

2008 2nd place at "Brain eXpert Competition" of GE Healthcare.

2006 Research Grant from Center of Neuroscience Zurich, University / ETH Zurich, Switzerland.

Peer-Reviewed Publications:

Van der Mark, S., Bucher, K., Maurer, U., Schulz, E., Brem, S., Buckelmüller, J., Kronbichler, M., Loenneker, T., Klaver, P., Martin, E. & Brandeis, D. (under review). The ventral visual stream in reading: evidence from functional connectivity patterns in dyslexic children and in controls.

Van der Mark, S., Bucher, K., Maurer, U., Schulz, E., Brem, S., Buckelmüller, J., Kronbichler, M., Loenneker, T., Klaver, P., Martin, E. & Brandeis, D. (under review). Children with Dyslexia lack multiple Specializations along the Visual Word form (VWF) System.

Schulz, E., Maurer, U., **Van der Mark, S.**, Bucher, K., Brem, S., Martin, E. & Brandeis, D. (under review). Reading for meaning in dyslexic and young children: distinct neural pathways but common endpoints.

Maurer, U., Bucher, K., Brem, S., Benz, R., Kranz, F., Schulz, E., **Van der Mark, S.**, Steinhausen, H.-C., Brandeis, D. (in press).

Neurophysiology in preschool improves behavioral prediction of reading ability throughout primary school. *Biological Psychiatry*.

Sack, A.T., **Van der Mark, S.**, Schuhmann, T., Schwarzback J. & Goebel, R. (2009). Symbolic action priming relies on intact neural transmission along the retinogeniculo-striate pathway. *NeuroImage 44(1)*: 284-93

Schulz, E., Maurer, U., **Van der Mark, S.**, Bucher, K., Brem, S., Martin, E. & Brandeis, D. (2008). Impaired semantic processing during sentence reading in children with dyslexia: Combined fMRI and ERP evidence. *Neuroimage 41(1)*: 153-68

Congress Posters / Abstracts:

Sanne van der Mark, Kerstin Bucher, Urs Maurer, Enrico Schulz, Silvia Brem, Jsabelle Buckelmüller, Martin Kronbichler, Thomas Loenneker, Peter Klaver, Ernst Martin, Daniel Brandeis (September 2008). Children with dyslexia lack multiple specializations along the Visual Word form (VWF) system. Poster presented at: Symposium of the Neuroscience Center Zurich.

Sanne van der Mark, Kerstin Bucher, Urs Maurer, Enrico Schulz, Silvia Brem, Jsabelle Buckelmüller, Martin Kronbichler, Thomas Loenneker, Peter Klaver, Ernst Martin, Daniel Brandeis (July 2008). Early Dysfunction of Specialization within the VWF-System is Associated with Dyslexia. Poster presented at: 6th Symposium of the Federation of European Neuroscience Societies (FENS), Geneva, CH

Sanne van der Mark, Kerstin Bucher, Urs Maurer, Enrico Schulz, Silvia Brem, Jsabelle Buckelmüller, Martin Kronbichler, Thomas Loenneker, Peter Klaver, Ernst Martin, Daniel Brandeis (October 2007). Functional activation, asymmetry and connectivity in a

posterior region linked to orthography and dyslexia. Poster presented at: Symposium of the Neuroscience Center Zurich.

Sanne van der Mark, Kerstin Bucher, Urs Maurer, Enrico Schulz, Silvia Brem, Jsabelle Buckelmüller, Martin Kronbichler, Thomas Loenneker, Peter Klaver, Ernst Martin, Daniel Brandeis (August 2007). Functional activation, asymmetry and connectivity in a posterior region linked to orthography and dyslexia. Poster presented at: Symposium of the Zurich Center for Integrative Human Physiology (ZIHP).

Sanne van der Mark, Kerstin Bucher, Enrico Schulz, Silvia Brem, Jsabelle Buckelmüller, Urs Maurer, Thomas Loenneker, Ernst Martin, Daniel Brandeis (April 2007). Differences in phonological processing in dyslexic & normal reading children. Poster presented at: University Children's Hospital Zurich Poster session.

Sanne van der Mark, Kerstin Bucher, Enrico Schulz, Silvia Brem, Jsabelle Buckelmüller, Urs Maurer, Thomas Loenneker, Ernst Martin, Daniel Brandeis (June 2007). Processing of pseudo-homophones and pseudo-words in dyslexic and normal reading children. Poster presented at: 13th Annual Meeting of the Organization for Human Brain Mapping, Chicago, U.S.A.

Sanne van der Mark, Kerstin Bucher, Enrico Schulz, Silvia Brem, Isabelle Buckelmüller, Urs Maurer, Thomas Loenneker, Ernst Martin, Daniel Brandeis (October 2006). Processing of pseudo-homophones in dyslexic and normal reading children. Poster presented at: Symposium of the Neuroscience Center Zurich.